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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

OCTOBER, 1930

ORIGINAL ARTICLES.

CLINICAL AND PATHOLOGICAL STUDIES ON SO-CALLED TUBULAR NEPHRITIS (NEPHROSIS).

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Many writers, believing that the histopathology of the kidney can be indicated with some degree of accuracy, when the history of onset and the distinctive clinical symptoms are correlated with the laboratory data, classify acute nephritis in children as: (1) Acute glomerular nephritis; (2) acute tubular nephritis; (3) acute "mixed" nephritis. This classification includes the common forms of acute nephritis seen in childhood and is supported by much pathologic evidence.

The clinical and laboratory data suggested as criteria for so separating the three different forms are as follows: (1) *Acute glomerular nephritis:* (*a*) A history of an acute infection antedating the onset; (*b*) hematuria; (*c*) visible or nonpitting edema; (*d*) increased arterial tension; (*e*) increased nonprotein nitrogen in the blood; (*f*) cerebral symptoms (uremia); (*g*) recovery. (2) *Acute tubular nephritis:* (*a*) Insidious onset without any antedating infection; (*b*) albuminuria, high specific gravity and lipoid bodies, casts and leukocytes, *no erythrocytes;* (*c*) marked pitting edema and ascites; (*d*) low plasma protein; (*e*) normal nonprotein nitrogen; (*f*)

normal arterial tension; (*g*) remissions and exacerbations; (*h*) termination with secondary infection. (3) *Acute "mixed" form* (in this group are placed those cases in which the onset, clinical course and laboratory data vary in one or more respects from characteristic features of 1 or 2). Examples of this are an insidious onset, with marked edema and albuminuria and elevated blood pressure, low plasma protein and normal nonprotein nitrogen or an onset following an acute infection, with a marked pitting edema, normal blood pressure, low plasma protein and alternating periods in which the urine shows an excessive albuminuria or *erythrocytes*, even *gross blood*.

As is generally known, the kidneys in the glomerular form are somewhat enlarged and the glomeruli are prominent. Practically all of the glomeruli are more or less involved. The tubules being an essential part of the renal unit, show changes which in all probability are secondary to, and to a large extent, dependent on the glomerular injury. The degree of fibrosis or scarring is directly proportional to the severity of the injury. When severe and continuous or recurrent, the process passes on to the development of the secondarily contracted kidney of adult life, the probable sequences being loss of renal tissue below functional adequacy, consequent hypertension and finally the development of the arteriolar degenerations characteristic of the primarily contracted kidney or so-called vascular nephritis. In acute tubular nephritis the notable changes in the kidneys are their increased size, the obscuring of normal markings and the presence of edema, pallor and opacity. Degenerative lesions are the characteristic feature. The proximal and distal convoluted tubules are the seat of diffuse degenerative changes with fat formation and there is cellular response only to such necrosis of tubules as may be present. The glomeruli are but slightly if at all involved, even when the process has continued for many weeks. In the mixed form of nephritis, the kidneys show lesions representative of both types.

Within recent years there has been much discussion concerning tubular nephritis, or nephrosis as termed by many authorities. Most of the contributions have come from adult clinics where the complexities surrounding the etiology and pathology are notably confusing. The most recent work on acute tubular nephritis in children has been reported by Davison and Salinger.[1] They present the clinical and laboratory findings with detailed pathologic studies in 4 patients. During the past five years, in children with acute nephritis, we have seen 21 cases which, according to the clinical and laboratory data, fulfill the requirements for the diagnosis of acute tubular nephritis. Ten of these patients died and necropsy was obtained in 8 patients.

The purpose of this communication is to report a clinical and pathologic study of 8 fatal cases of acute tubular nephritis in

ANALYSIS OF DATA OF EIGHT CASES OF ACUTE TUBULAR NEPHRITIS.

Case No.	Age at death.	Duration.	Remissions.	Clinical diagnosis.	Exceptions.	Terminal events.	Ratio to normal kidney weight.	Histology.
I	3½ yrs.	2½ yrs.	6	Acute tubular nephritis	Occasional R.B.C. in urine	Hemolytic streptococcus peritonitis	236 104	Cicatrices; hyalin droplets; mitoses
II	3 yrs., 11 mos.	6 mos.	2	Acute tubular nephritis	Initial high B.P.; Nervous origin?	Hemolytic streptococcus peritonitis and pleuritis	333 104	Cicatrices; hyalin droplets
III	6 yrs.	4 mos.	2	Acute tubular nephritis	Typical case	Hemolytic streptococcus peritonitis	200 132	Cicatrices; necrosis and regeneration
IV	1 yr., 11 mos.	6 mos.	3	Acute tubular nephritis	Slight increase in B.P.; slight increase in N.P.N., 56 mg.	Hemolytic streptococcus septicemia	259 93	Cicatrices; hyalin to necrosis; streptococcus; emboli in glomerulus
V	2 yrs., 3 mos.	3 mos.	0	Acute tubular nephritis	Onset with acute infection; coryza and fever	Acute streptococcus peritonitis and pleuritis	128 96	Granular degeneration to rare necrotic cell; fat
VI	2 yrs., 2 mos.	5 wks.	0	Acute tubular nephritis	Onset with acute infection; coryza, vomiting, fever, rapid course	Pneumococcus pleuritis and peritonitis	92 93	Granular degeneration and hyalin droplets
VII	3 yrs., 8 mos.	?	0?	Acute tubular nephritis	Typical case	Streptococcus (?) peritonitis	176 114	Hyalin to complete necrosis
VIII	1 yr.	8 mos.	2	Glomerular tubular nephritis	Terminal high B.P. 120 to 170 100 105	Pneumococcus septicemia; Streptococcus viridans peritonitis	138 88	Granular degeneration; fat

children, with a view of ascertaining the accuracy with which a pathologic diagnosis can be determined from a consideration of the clinical and laboratory data. The essential clinical and laboratory features have been reviewed and from them an opinion as to the underlying pathologic process has been expressed. The accuracy of the clinical diagnosis has then been checked with the histologic findings.

The criteria taken as indications for degenerative lesions in the uriniferous tubules, without glomerular or interstitial changes, have been mentioned above. Any deviations from the characteristic findings have been regarded as exceptions to the rule and suggest that glomerular lesions with or without interstitial changes exist.

The character of the material of this report is outlined in the table on page 453. In the column of kidney weights the upper figure is the combined weight of the kidneys; the lower figure is the average of normal weight of both kidneys for corresponding age.

If the before-mentioned clinical and laboratory criteria are rigidly followed in establishing the diagnosis of acute tubular nephritis, only 2 of the 8 cases can properly belong to this form of nephritis. They are Case III and Case VII. It is true, the other 6 cases show only slight or minor departures from the so-called pathognomonic signs, such as: Case I, the finding occasionally of a few erythrocytes, microscopically in the urine; Case II, an initial high blood pressure which subsequently became normal; Case IV, a slight increase of blood pressure and a slightly increased nonprotein nitrogen; Case V, an onset of edema and albuminuria with an acute infection; Case VI, an onset with an acute infection and with rapidly progressing widespread terminal infection; Case VIII, an onset with vomiting and edema at fourteen months, again at sixteen months, at twenty-one months, edema and albuminuria and increasing blood pressure. These minor variations from the criteria characterizing tubular nephritis were considered by us to be of importance as possibly indicating the presence of kidney lesions not repairable by simple regeneration of tubular epithelium. However, we have not been able to find significant differences in the pathology of the 8 cases and have discarded the hope of giving prognostic value to the type of information presented.

Case Histories. CASE I.—The patient, N. G. (Hospital No. 10109), was under observation from the onset of albuminuria and edema at nineteen months of age until he died of generalized peritonitis, when three and a half years of age. When first seen he had been ill for two weeks with generalized edema, and albuminuria. Insofar as could be ascertained, the edema was not preceded by an acute infection, and physical examination revealed no evidence of a local or general infectious process. The *temperature* was 105° F. on admission but remained normal throughout his stay in the hospital (four months) with one exception, when it rose to 103° F. for five days. No explanation was found for the fever at that time. During his stay in the hospital there were two periods in which the edema practically dis-

appeared; the urinary output increased and there was a lessened albuminuria. In the first period he lost 5½ pounds in six weeks; in the second period he lost 5 pounds in eight weeks. At the end of this period he was discharged much improved. Albumin and cellular elements, however, continued to be found in the urine. Various measures to influence the edema were tried without striking results. He remained at home eight months. In this interval, the course was characterized by remissions and recurrences of edema. The edema became excessive during an attack of mumps, and the daily urinary output dropped from an average of 560 to 620 cc. to 120 to 150 cc. The urine continued to contain albumin and cellular elements. On the second admission (one year after onset) he showed generalized edema and albuminuria over a period of three months. No evidence of local or generalized infection could be found. There was one remission in which he lost 5 pounds in two weeks. Thereafter the edema remained stationary until, without apparent cause, it entirely disappeared. The effects of high-protein diet were tried as on the former admission without noteworthy results. There was a lessened amount of albumin and fewer cellular elements in the urine when he was again discharged. Following this discharge his general health and appearance remained good but there was always a slight trace of albumin in the urine. During the winter he had diphtheria. The edema and albuminuria returned, but gradually disappeared. He was admitted for the third time (nearly one year after second admission but almost exactly two years after the original onset) because of a recurrence of the edema and albuminuria. These symptoms had recurred two weeks before and were definitely associated with an acute respiratory infection and an acute parotitis. The temperature fluctuated between 98° F. and 100° F. The patient was observed in the hospital over a period of four months during which various therapeutic measures were tried. Calcium chlorid resulted in a temporary loss of weight but repetition of the course of treatment had no effect. Ammonium chlorid was likewise without benefit. The protein content of the diet was increased; the child continued to gain weight and theocin and caffein were given. These measures had no effect on the edema. In 6 days the weight increased from 36 pounds to 38¾ pounds. Caffein was omitted and the patient was given diuretin. The edema continued to increase; three days later the weight reached 40 pounds and was then stationary. The protein in the diet was increased to 60 gm. and subsequently to 70 gm. This change in diet seemed to have some effect on the edema. He was discharged free from edema three weeks later weighing 31½ pounds. Albumin and cellular elements remained present in the urine. A few days after discharge, although he was kept on the high-protein diet, the urinary output began to diminish and the edema to recur. He was returned to the hospital (fourth admission) for this reason. The *temperature* varied between 99° F. and 102° F. for ten days. It then rose rapidly and remained about 102° F. to 104° F. until he died, twelve days later. With the terminal rise in temperature, the edema increased markedly and the patient complained of pain in the region of the right kidney. Tenderness became marked in this region as well as over the abdomen. With the question of a perinephritic abscess or a generalized peritonitis in mind, an exploratory incision was made over the right kidney. Pus was not found. The kidney capsule was stripped (Edebohl's operation) without any benefit to the patient. He rapidly became worse and died a few days later. *Non-hemolytic* streptococcus was recovered from the peritoneal fluid.

Laboratory Data. First Admission. The white blood cells were 24,900 per c.mm., 75 per cent were polymorphonuclear in type. *Urine:* Specific gravity, 1020 to 1032; albumin (0.5 to 1 gm. per cent); granular and cellular casts; many white blood cells; an occasional red blood cell; N.P.N., 30 mg. per 100 cc.

Phenolsulphonephthalein test, 75 per cent (two and a half hours). *Plasma protein*, 5.75 per cent. *Fixation test* normal.

Second admission. Urine: Specific gravity, 1020 to 1035; albumin, 4.8 gm. per cent; hyalin and granular casts and white blood cells. White blood cells 16,000 to 40,000 (60 per cent polymorphonuclears); N.P.N., 28 mg. per 100 cc.; chlorids, 533; cholesterol, 397; *serum protein*, 5.23; blood pressure, 100/60; *phenolsulphonephthalein*, 40 per cent.

Third Admission. Urine: Specific gravity 1010 to 1020; albumin, 3 gm. per cent; many hyalin and granular casts and white blood cells; *blood pressure*, 110/60 to 65/40.

Summary (by Dr. Blackfan before the autopsy). The diagnosis of acute tubular nephritis was made by the appearance of albuminuria and edema without an antecedent infection and without evidences of a focus of infection, by exacerbations, sometimes but not always initiated by an intercurrent infection and by remissions, at which times the patient was free from symptoms, together with the termination by hemolytic streptococcus peritonitis. The clinical findings when correlated with the laboratory data which showed a normal nonprotein nitrogen, a low serum protein, an albuminuria, normal phenolsulphonephthalein and a normal blood pressure, support the impression that the outstanding lesions found would be degenerative changes in the tubules. The finding of a few red blood cells in the urine from time to time may mean slight changes in the glomeruli.

Autopsy (A-24-115). Four and a half hours postmortem, restricted to the abdomen.

The condition of the heart and lungs was not ascertained.

There was an acute peritonitis which proved to be due to an hemolytic streptococcus. The spleen showed irrelevant changes.

The gastrointestinal tract showed no lesions.

The pancreas was normal in gross and upon microscopic examination.

The liver weighed 420 gm. It showed a fine yellowish mottling. The color as a whole was pale and cut surfaces were cloudy in appearance. The gall bladder and bile passages were normal. Microscopically there was a moderate degree of fatty infiltration in the form of large drops at the peripheries of the lobules. The liver cells throughout were reduced in size and showed marked acidophilic staining, fine vacuolization and there was much granular débris between liver columns and sinusoids. There was much separation of liver cells so that the columns appeared disorganized. No necroses.

The adrenals were small; microscopically they showed congestion and a marked diminution of cortical lipoid.

The bladder and genitalia were normal.

The kidneys: The right weighed 116 gm., the left 120 gm. They were enlarged, pale, succulent with obscured markings. The cortex measured 0.5 cm. to 0.7 cm. in depth and was finely mottled with opaque yellowish lines and dots. The glomeruli were visible with difficulty as red points.

Microscopic Examination. The glomeruli were essentially normal. A few showed an increase of cells in the capillaries, polymorphonuclear leukocytes and mononuclear cells presumably from the endothelium; attributed to the effects of the streptococcus peritonitis.

The convoluted tubules throughout the many sections taken from both kidneys showed striking change. The proximal convoluted tubules were dilated and occasionally infolded, and usually contained much granular detritus and circular reticulum. The epithelial cells were either swollen or diminished in size, the cytoplasm granular and finely vacuolated and occasionally with colloid droplets. Some swollen granular cells seemed to be discharging portions of their cytoplasm into the lumen of the tubule; elsewhere the cells were much reduced in size. The nuclei in general were

normal and cells showing evidence of actual necroses were rare. Mitotic figures were occasionally found. The distal convoluted tubules showed similar but less striking changes. The Henle's loops showed slight or doubtful changes. The collecting tubules showed finely vacuolated cells. The Henle tubules, distal convoluted and collecting tubules contained many deeply staining casts of hyalin material. In the cortex were a few minute cicatrices, most of them of compact fibrous tissue. Some, however, contained many lymphoid and plasma cells and rarely one contained a residuum of necrotic tubule. Occasionally such cicatrices were in contact with fibrosed glomeruli. These cicatrices we interpreted as the result of repair following complete necrosis of tubules.

Fat stains showed considerable amounts of fat in the convoluted and collecting tubules in the form of small droplets. Most of the fat stained deep red with Scharlach R, and pink or red with Nile-blue sulphate.

The important lesions of these kidneys were in the convoluted tubules. The slight glomerular changes were those usually with an acute streptococcus infection. In spite of the clinical evidence of long standing, recurrent renal disturbance, the microscopic study has revealed only a rare minute cicatrix and lesions which were degenerative in type and which can be produced experimentally in a comparatively few days.

Case II.—C. P., aged three and a half years (Hospital No. 100113) was observed over a period of six months. He was admitted to the hospital five weeks after an insidious onset with edema, ascites and albuminuria. After three months he was discharged, much improved. He remained apparently well for two weeks, when following an acute respiratory infection, he was returned with the edema and albuminuria as advanced as at the previous entry. Two months later he was exposed to measles and was sent to the contagious division. The edema subsided and he remained free from symptoms for one month, then he was returned to the hospital because of recurrence of the edema, albuminuria, fever and abdominal pain. He died three days later with an hemolytic streptococcus peritonitis.

Laboratory Data. Urine: Specific gravity, 1025; large amount of albumin; no red blood cells; hyalin and granular casts. *Blood:* 25,000 white blood cells, 68 per cent polymorphonuclear; *plasma protein*, 3 to 5 per cent; N.P.N., 30 mg.; blood pressure at the first admission was 150/100, remaining high for several days, then varying around 90/60 mm.

Summary (by Dr. Blackfan before the autopsy). One would hesitate in this case to infer from the initial blood pressure alone at the first admission, especially with the subsequent normal blood pressure findings, that this finding indicated glomerular involvement. The element of nervous influence on blood pressure in children always needs to be considered. The clinical course and laboratory data would support the belief that the outstanding histological changes would be in the kidney tubules.

Autopsy (A-27-74). Two hours postmortem. The immediate cause of death was acute peritonitis and pleuritis due to an hemolytic streptococcus.

Heart: Weight, 75 gm. It showed no relevant or important lesions.

Lungs: Weight, right, 160 gm.; left, 115 gm. Both lungs showed acute bronchitis and bronchopneumonia grossly and microscopically. The pneumonic process proved to be of the infiltrating type with peribronchitis and interstitial pneumonitis, with numerous recent thrombi in bloodvessels. Many streptococci were present in the vessel walls and in the thrombi.

Gastrointestinal tract: The gastrointestinal tract was negative grossly and microscopically.

Pancreas: Negative in gross and microscopically.

Liver: Weight, 925 gm. The gross appearance was not remarkable. Microscopically there was a moderate infiltration of peripheries of lobules

with fat in the form of large drops. In addition, throughout the liver the cells were finely vacuolated and the cytoplasm filled with deeply eosin-staining granules with occasional cells containing a basic staining reticulum. There was much débris between the liver columns and sinusoids, the latter contained an excess of polymorphonuclear leukocytes and large mononuclear phagocytes. These appearances were interpreted as acute changes, presumably due to streptococcus toxins and to be characterized as cloudy swelling or acute parenchymatous degeneration.

Adrenal glands: Grossly negative; microscopically they showed a marked diminution of cortical lipoid and occasional foam cells. The medulla was normal.

Bladder and genitalia: Normal.

Aorta showed a few minute atheromatous patches in the ascending portion.

Organs of the neck: Normal.

Brain: Weight, 1200 gm. Markedly edematous.

Kidneys: Weight, right, 158 gm.; left, 175 gm. They were enlarged, soft, succulent, pale yellowish-brown. On section the parenchyma everts from the capsule. The markings were obscured. The cortex measured 1 cm. in width, flecked with minute opaque-yellow areas and demarcated by a band a few millimeters wide at the base of the pyramids of opaque yellow. The pelves and ureters showed no lesions and were apparently normal.

Microscopically, there were lesions of two distinctly different periods, one represented by numerous linear cicatrices containing atrophic tubules and infiltrated with lymphoid and plasma cells. In the proximity of the cicatrices were occasional fibrosed or fibrosing glomeruli. Some of the atrophic tubules contained polymorphonuclear leukocytes and the appearance suggested involvement of the kidney secondary to an infection of the pelvis. The pelvic epithelium was intact, but beneath it was a moderate lymphoid and plasma-cell infiltration. It is probable that this late lesion was secondary to severe degenerative lesions of the tubules.

The second type of lesion was very striking and uniformly distributed; a degeneration of the epithelium of the convoluted and ascending Henle tubules. The convoluted tubules were markedly dilated, oftentimes the epithelium was infolded. The epithelium in most of the tubules was greatly swollen, finely vacuolated and filled with eosin-staining granules. Occasionally there was a regenerating cell, rarely a completely necrotic cell invaded by leukocytes. There were numerous pyknotic nuclei. The distal convoluted tubules and ascending Henle tubules frequently showed rather large densely staining hyalin globules basally situated. Also there was evidence of edema of the interstitial tissues throughout the kidney. There were many deeply staining casts of hyalin material in tubules of various types. The glomeruli were practically normal. A few contained migrating leukocytes, probably the first evidence of recent damage due to the streptococcus infection. Scharlach R stains showed much less fat than the gross appearance of the kidney suggested. Tubules of all types showed a moderate amount of fat in the epithelial cells. In some groups of convoluted tubules it was excessive in amount. Such tubules were usually those with flattened epithelium. There was a small amount of fat fairly uniformly distributed in the ascending Henle tubules and in the collecting tubules. This kidney summarizes as follows:

1. Evidence of a healed destructive lesion, presumably repair after destruction of tubules.
2. Severe tubular nephritis with intact glomeruli.

As in Case I, it is impossible to correlate the apparently recent injury of the tubules and the history of six months' illness. Both middle ears con-

tained pus in which were long-chained streptococci. The drums were dull colored and thickened.

CASE III.—W. C., aged five and a half years (Hospital No. 77165) was admitted to the hospital on November 17, 1924. Two months previously the mother noticed that his eyes were swollen and that he was irritable and had anorexia. The physician found albumin, casts and leukocytes in the urine. Insofar as could be ascertained no acute infection preceded the edema and albuminuria. The *examination* was negative except for the generalized edema and ascites.

Course in the Hospital. Temperature varied between 98° and 100° F. during his stay in the hospital, with the exception of two separate occasions when it rose to 103° and 101° F. No cause was determined for these rises which lasted each time less than twenty-four hours. *Edema:* He weighed 42 pounds on admission. He gained 2 pounds in weight during the first week of his stay in the hospital and then remained at this weight for the following two weeks. During this time he was given calcium chlorid over a period of three days. This was followed by small doses of sodium bicarbonate (1 gm. twice daily). These measures did not influence the edema nor the urinary output. The edema, however, was materially influenced, as shown by decrease in weight and urinary output, when the dose of sodium bicarbonate was increased to "1 gm. four times a day." *Intake and output* rose from 1000/780 to 1000/1300. The weight fell from 43½ to 38 pounds. The tonsils and adenoids were removed and he was discharged after having been under observation about six weeks. There was no edema, the very slightest trace of albumin, and there were no cellular elements in the urine.

Subsequent Course. Three days after his return home, he developed an acute respiratory infection. This was followed by an increase in the edema. He remained in bed, but was returned to the hospital after a month—February 11, 1925, inasmuch as the edema increased and the urinary output diminished (1200/290).

Examination on return revealed nothing abnormal except the marked edema. The temperature on admission varied between 99 and 101° F., and six days after admission rose to 105° F. At that time peritonitis was suspected because of abdominal pain. On account of rapidly increasing fever and abdominal distention, an exploratory operation seemed advisable. peritonitis was found.

Laboratory Data (first admission). *Urine:* Specific gravity, 1008 to 1012; albumin ++. The sediment contained an occasional granular and hyalin cast. *Blood:* Erythrocytes, 5,000,000; hemoglobin, 90 per cent; white blood cells, 17,000 (45 per cent polymorphonuclears); phthalein test, 55 per cent; N.P.N., 47 mg. per 100 cc.

Laboratory Data (second admission). The urine showed a large amount of albumin with a few hyalin and granular casts. N.P.N. was 29.2. The *blood pressure* remained around 95/60. The *culture* from the purulent fluid showed nonhemolytic streptococcus. The patient died.

Summary (by Dr. Blackfan before autopsy). The diagnosis of acute tubular nephritis was made by the insidious onset without an antecedent infection and edema, the remissions and the terminal infection of a nonhemolytic streptococcus peritonitis. The urine contained albumin, hyalin and granular casts, white blood cells and no red blood cells, the nonprotein nitrogen and phenolsulphonephthalein test were normal as well as the blood pressure. Therefore the correlation between the clinical course and the laboratory data would suggest histologic changes involving the kidney tubules without manifestations in the glomeruli.

Autopsy (A-25-24). The postmortem examination, made one hour after death, was restricted to an inspection of the abdomen through the surgical incision and removal of the kidneys for histologic study.

There was a diffuse fibrinopurulent peritonitis. An hemolytic streptococcus was cultivated from the exudate.

The liver was large, firm, low in position. The spleen enlarged, soft and pulpy. The kidneys weighed each 100 gm. They were large, pale, mottled with yellow, and unusually soft. On section the parenchyma was soft, succulent and bulged from the capsule. The cortices measured 1 cm. in width. The color was opaque, yellowish, mottled with red throughout the cortices. The glomeruli were prominent as red dots. The pyramids were injected, their apices deep red in color. The capsules stripped with slight difficulty and left slightly granular surfaces. The pelves and ureters were normal.

Microscopic Description. Twenty-two blocks from both kidneys showed identical appearances. Severe tubular degeneration and occasionally necrosis of tubules with practically intact glomeruli characterized the kidneys. The lesions affected chiefly the convoluted tubules and the ascending loops of Henle's tubules. The epithelium of the tubules exhibited all degrees of damage from cloudy swelling to complete necrosis. The proximal convoluted tubules showed large vacuoles basally situated in the cells in great numbers. These were filled with fat which stained red with Scharlach R and pink with Nile-blue sulphate. With polarized light most of the fat proved to be isotropic, only occasional droplets proved doubly refractive. While the fat vacuolization was heaviest in the convoluted tubules, actual necrosis of their cells was rare. The distal convoluted tubules, ascending Henle tubules showed greater swelling and granulation of cells and there were many systems of tubules with nearly every nucleus in a pyknotic condition. There were a few tubules filled with desquamated necrotic cells, invaded by polymorphonuclear leukocytes and surrounded by lymphoid and plasma cells and polymorphonuclear leukocytes. In convoluted tubules there were occasional cells containing deeply stained acidophilic hyalin coagula somewhat similar to the picture found in corrosive sublimate poisoning. Rarely were mitotic figures found in the tubular epithelium. The glomeruli in general were intact. A few only showed an increase of cells in the capillaries, rarely one with hyalin thickening of the cement substance of the capillary walls. Scattered through both kidneys were very small cicatrices, rarely larger than could be accounted for by the disappearance of a single tubule, most of these cicatrices contained lymphoid and plasma cells and could be explained as the consequence of the reactions following necrosis of tubules—an explanation which probably accounted for the change in occasional glomeruli. Tubules of all varieties contained material in sequence of cast formation, granular débris and circular reticulum in the proximal convoluted tubules, granular and deeply staining hyalin casts in Henle loops and distal convoluted tubules. With polarized light, fatty acid crystals and doubly refractive globules were found in the casts in frozen sections.

Case IV.—S. L. (Hospital No. 10983), a male, aged twenty months, was regarded as a normal infant until the onset of the present illness. This began insidiously three months before admission to the hospital with edema and suppression of urine. No acute infection, so far as could be ascertained, preceded the onset of the edema. The examination revealed an extremely edematous infant with free fluid in the peritoneal cavity and slightly elevated blood pressure.

Course in the Hospital. Urinary output—during the first twenty-four hours in the hospital the patient voided but once. Thereafter the urinary output appeared in fair proportion to the intake of fluid. The *temperature* ranged around 99° to 103° F. for twelve days, after which it remained normal for six weeks. It became elevated then, varying from 98° to 104° F.

for seven days. Following an interval of normal temperature for twelve days, it rose to 104° F. where it remained until the end.

Infection. Every effort to find a focus of infection was unsuccessful until three days before last febrile period, when an abscess developed in the region of the left scapula. This was opened and drained. Its point of origin was not determined. Streptococcus hemolyticus was cultured from the pus. In so far as could be determined by roentgenogram, there were no evidences of sinus infection. *Weight:* The patient weighed 32 pounds 10 ounces on admission. At no time was he entirely free from edema. There were three periods in which the weight and, therefore, the edema decreased materially. The first period followed the administration of magnesium sulphate, 50 per cent solution, 32 to 45 gm. daily. He lost 7 pounds in two weeks, (32.10 to 24.6 pounds). The second period followed the administration of ammonium sulphate. He lost 5 pounds in fifteen days (34.4 to 29.14 pounds). The third period followed the terminal fever which continued for four days. He lost 1 pound 4 ounces (29 to 27.12 pounds).

Albumin. During the administration of magnesium sulphate by mouth, with the rapid lessening of the edema, the albumin appeared (qualitatively estimated) to be less in amount and there were fewer formed elements in the urine. Throughout the course of the illness the quantitative amount of albumin rose from 4.8 gm. per liter to 7 gm. The *blood pressure* fell from 105/70 to 90/55 during the rapid loss in weight. *Temperature:* The weight and amount of albumin were not influenced by the fever except at the terminus when there was a rapid loss of weight.

Laboratory Data. Urine: Marked amount of albumin, many hyalin and granular casts and many leukocytes; no erythrocytes. *Phenolphthalein* 40 per cent in two hours (intravenous); N.P.N., 55 mg.; *serum protein* (venous blood), 5.8 per cent; *albumin*, 7 gm. per liter; white blood cells, 19,000 (50 per cent polymorphonuclears). The blood pressure was 108/70 on admission.

Summary (by Dr. Blackfan before the autopsy). The onset with generalized edema and albuminuria with remissions and exacerbations continuing over a period of six months terminating fatally with an hemolytic streptococcus septicemia when correlated with the presence of 7 mg. of albumin in the urine, a normal phenolphthalein excretion and a low serum protein, would lead one to believe that the chief histologic changes would be found in the renal tubules. The exceptions which might point to glomerular involvement were the slightly raised blood pressure on admission (108/70 as to the normal for the age 80/40) and the slight increase of the total nonprotein nitrogen (56 mg.).

Autopsy (A-24-40, one hour postmortem). Blood not examined. There was generalized edema, hydrothorax and ascites. The immediate cause of death was septicemia (hemolytic streptococcus) presumably secondary to the scapula abscess.

The *heart* weighed 69 gm. Microscopically it showed a moderate interstitial edema.

Lungs. The left weighed 82 gm., the right 98 gm. Both were crepitant and were normal in appearance except for congestion of the lower lobes. The trachea and larger bronchi were normal. Microscopically the lungs were remarkable for the many thrombi in bloodvessels of all sizes. In a few arteries of medium size there were organizing thrombi. In many small arteries and veins there were recent thrombi and in the capillaries of alveolar walls there were great numbers of recently formed thrombi, these were both mural and occluding. The former were often composed of platelets and fibrin, the latter of fibrin in coarse strands or in fused hyalin masses. In the capillaries fused red blood corpuscles acted as thrombi free

and within phagocytic cells. In and adjacent to the thrombi in all locations were polymorphonuclear leukocytes and mononuclear phagocytes in varying numbers. The latter often contained pairs and chains of micrococci (Giemsa stain) and in a few instances there were masses of streptococci adherent to the intima of the vessel walls. Large portions of the many sections taken for study were bloodless, the capillaries in the alveolar wall being either thrombosed or packed with large mononuclear cells (phagocytes).

The *spleen* weighed 100 gm. Microscopically it showed collections of phagocytic cells in the centers of the follicles and in the pulp. The splenic veins and sinuses contained a remarkably large number of recent thrombi in composition like those in the lung and occasionally accompanied by streptococci.

Pancreas. Normal.

The *liver* was enlarged. It extended 7.5 cm. below the costal margin, 8.5 cm. below the tip of the ensiform cartilage.

Microscopically, it showed numerous focal necroses and a diffuse degeneration of the liver cells accompanied by a general infiltration with polymorphonuclear leukocytes. In places the continuity of the liver columns was disrupted giving a picture reminiscent of the liver of spirochetal jaundice. The liver cells were shrunken, the cytoplasm of many stained deeply with eosin, most of the cells contained basic staining reticulum and were often vacuolated. The nuclei for the most part appeared viable. In the sinusoids were numerous fibrin thrombi and many mononuclear phagocytes often enclosing polymorphonuclear leukocytes. The bile ducts were normal.

Adrenal Gland. Normal in gross and microscopically. There was considerable lipoid vacuolization of the cortical cells.

Kidneys. Left weighed 139 gm., the right 120 gm., were markedly enlarged, pale (light pink), soft, succulent. On incision the parenchyma everted from the capsule, which stripped easily. The markings of the section were obscured, cortex pale, glomeruli visible with difficulty as colorless points, the pyramids injected, the pelves and ureters normal.

Microscopically, the outstanding feature was severe and uniformly distributed degeneration of the epithelium of the convoluted and Henle tubules. Fat stains showed very little fat in the form of fine droplets almost exclusively in the distal convoluted tubules. By stains and polarized light this fat proved to be neutral fat. The tubular epithelium was everywhere swollen and granular and the lumena filled with circular reticulum and granular detritus and in places seemed to be discharging cytoplasm into the lumena in the form of budlike processes. In many places the degeneration was more severe and the cells were filled with colloid drops or reduced to narrow granular fringes. Actual death of cells was evidenced frequently by pyknotic nuclei and there were scattered tubules with completely desquamated epithelium, invaded and surrounded by leukocytes. This account applies to the convoluted and ascending Henle tubules. Densely stained hyalin casts were abundant in tubules of all types. The glomeruli were mostly normal. Numerous ones, however, contained small hyalin thrombi in the capillaries or fibrin thrombi in the arterioles, accompanying this there was a cellular response on the part of polymorphonuclear leukocytes and endothelium. In addition a few glomeruli showed the presence of polymorphonuclear leukocytes and hyalin thickening of the capillary walls without demonstrable thrombi. Rarely there was a glomerulus with proliferation of the capsular epithelium and complete occlusion of the tuft capillaries by mononuclear cells. In the cortex were numerous minute cicatrices often infiltrated with lymphoid and plasma cells.

The glomerular lesions of the kidneys were interpreted as due to the streptococcus infection and principally of embolic or thrombotic origin, and as representing the renal participation of processes seen in the lungs,

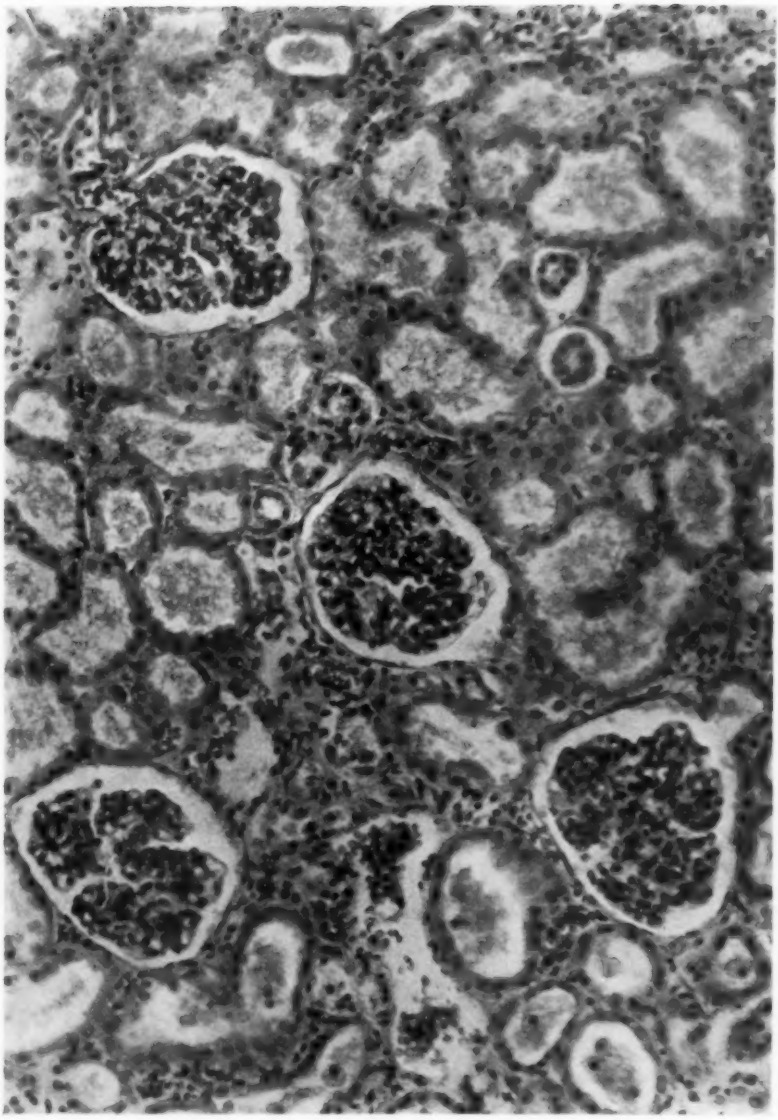

FIG. 1.—Kidney, Case V. Albuminuria and edema for three months. Note the normal appearance of glomeruli and evidences of moderate degeneration of tubular epithelium.

FIG. 2.—Kidney, Case IV. Duration of disease six months with three remissions. Colloid droplets in convoluted tubule epithelium.

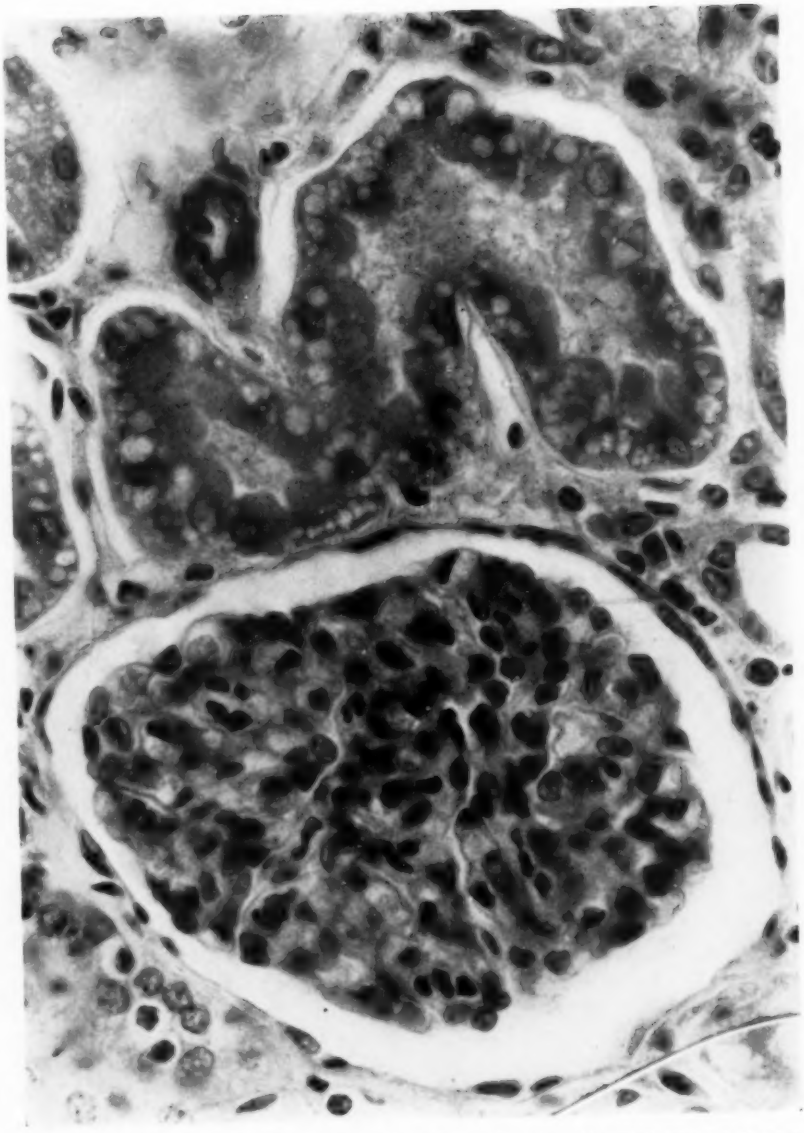

FIG. 3.—Kidney, Case III. Duration of disease four months with two remissions. Note normal glomerulus. To show marked fat vacuolization of epithelium of convoluted tubules.

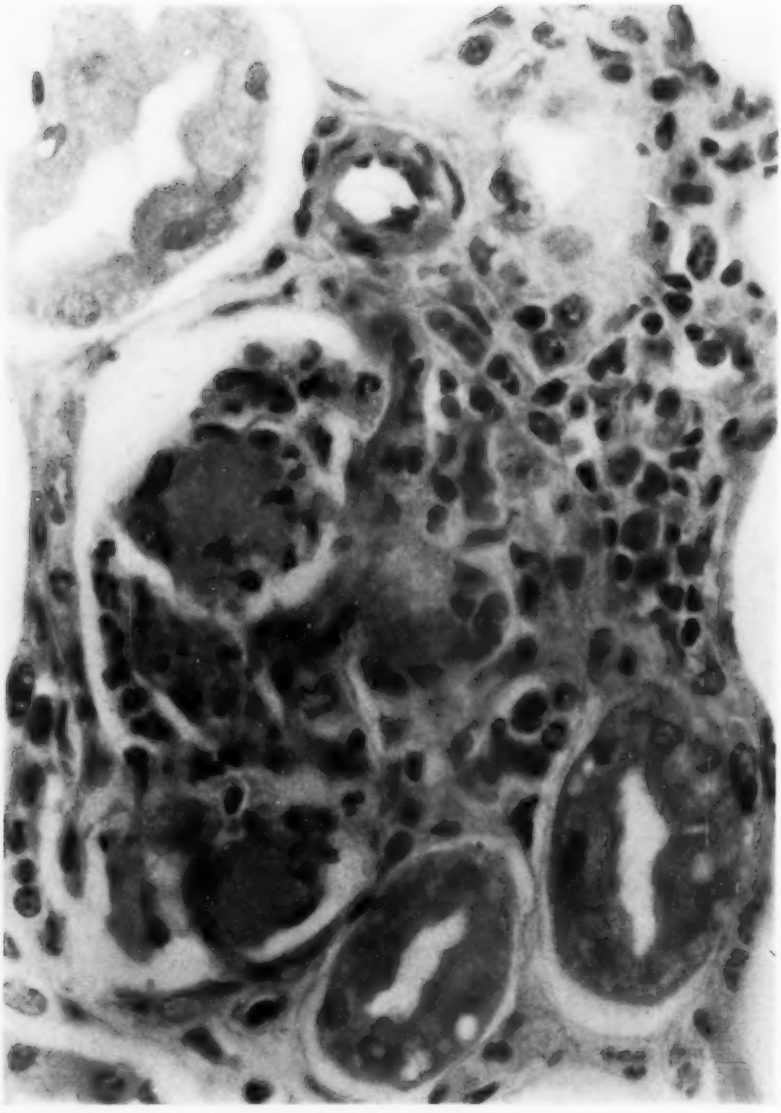

FIG. 4.—Kidney, Case III. Another field showing complete necrosis of a convoluted tubule and consequent reaction in the interstitial tissue.

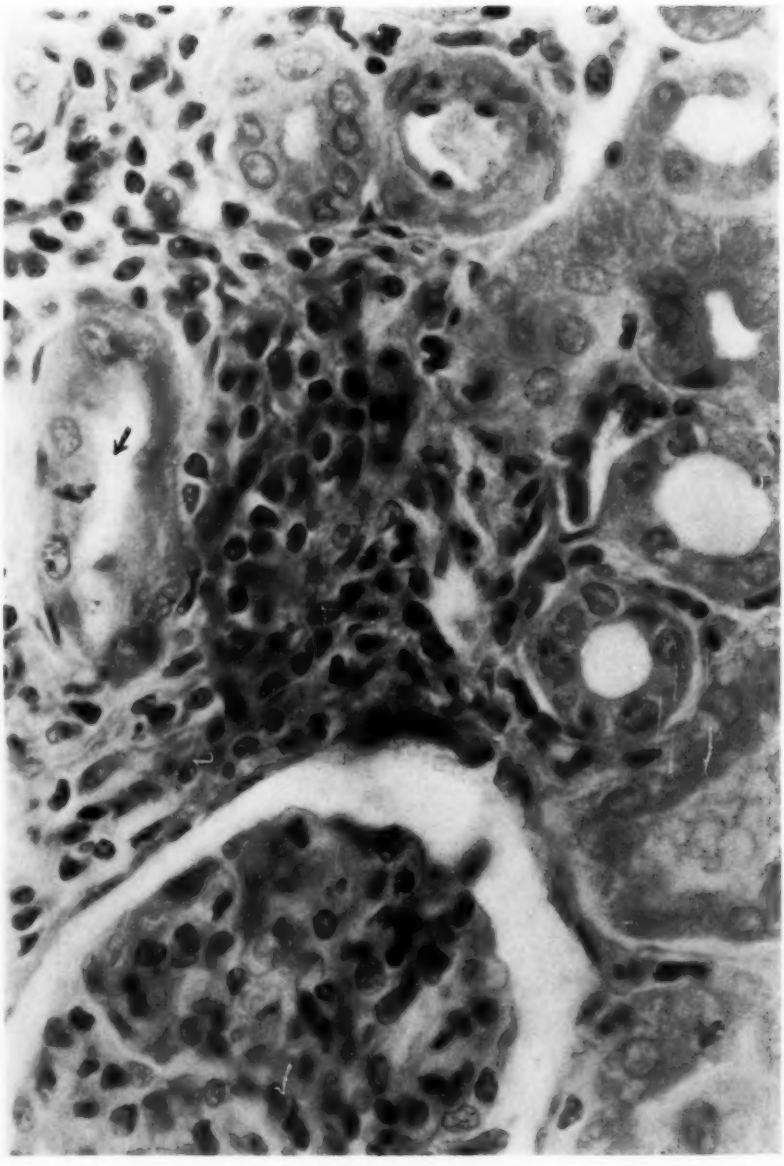

FIG. 5.—Kidney, Case III. Another field to show an early cicatrix resulting from the complete necrosis of a convoluted tubule. Above is a convoluted epithelial cell in mitosis.

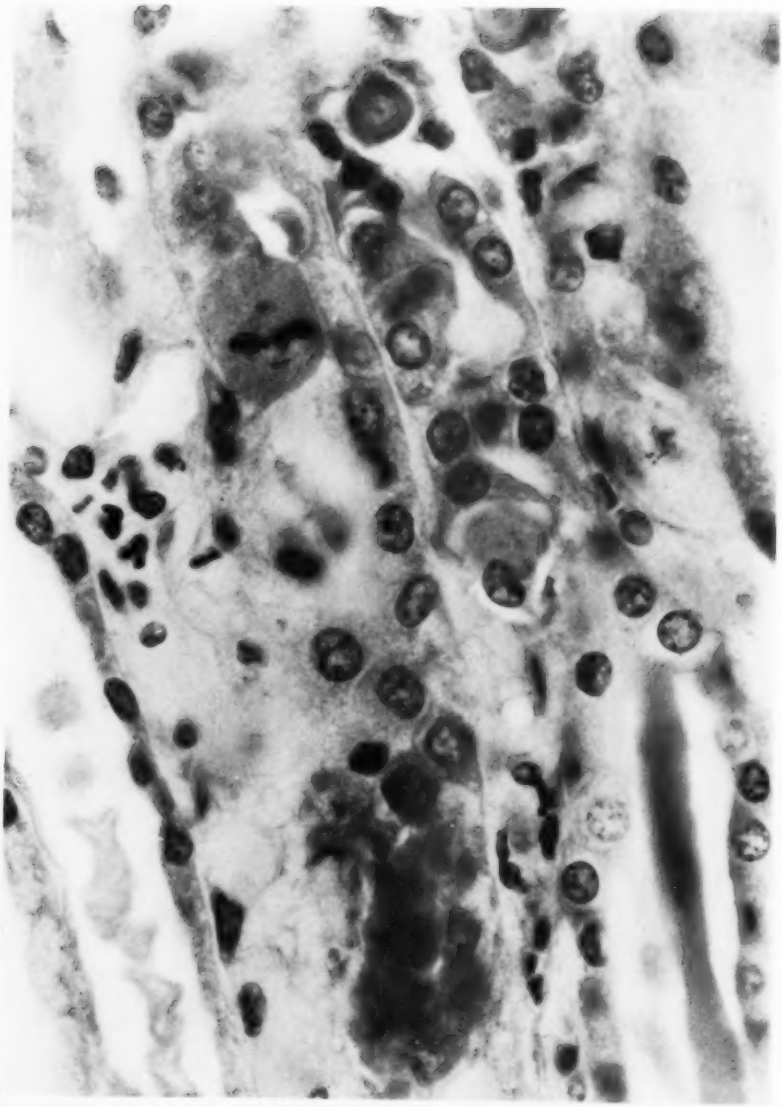

FIG. 6.—Kidney, Case VII. To show a severe grade of degeneration and necrosis of convoluted tubules and regeneration by mitotic division of epithelial cells.

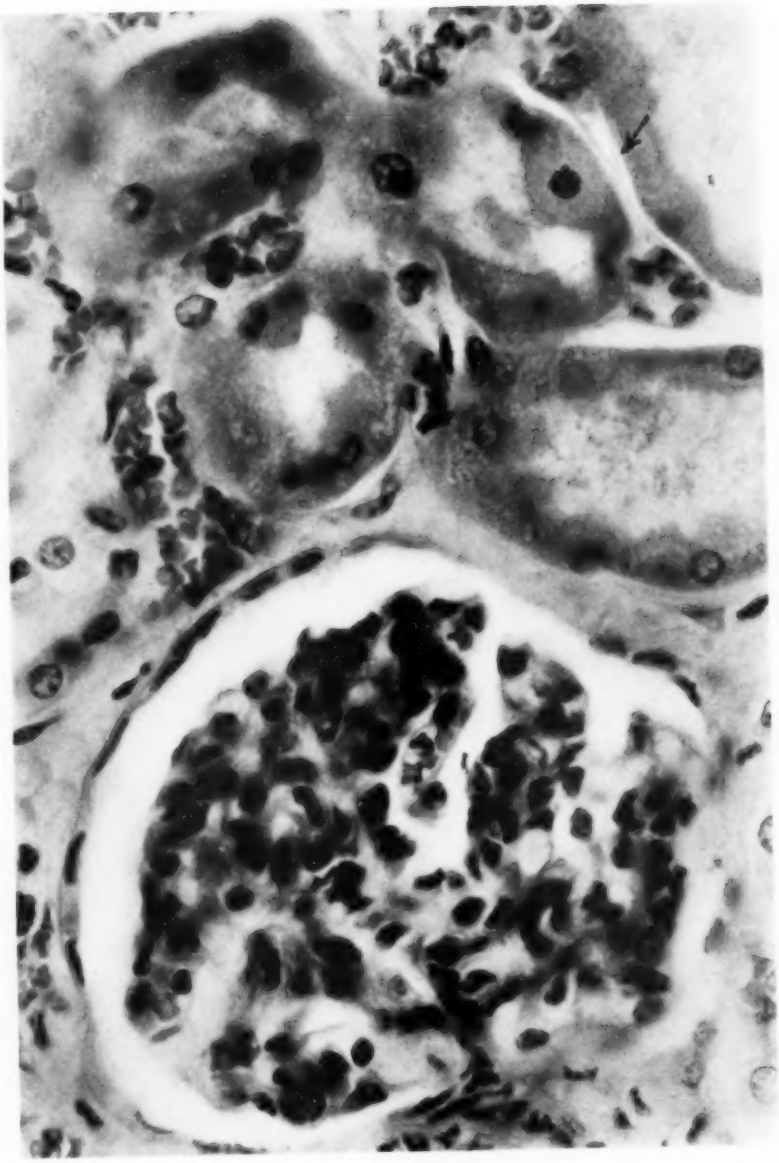

Fig. 7.—Kidney, Case VII. To show normal glomerulus and mitoses in convoluted tubules.

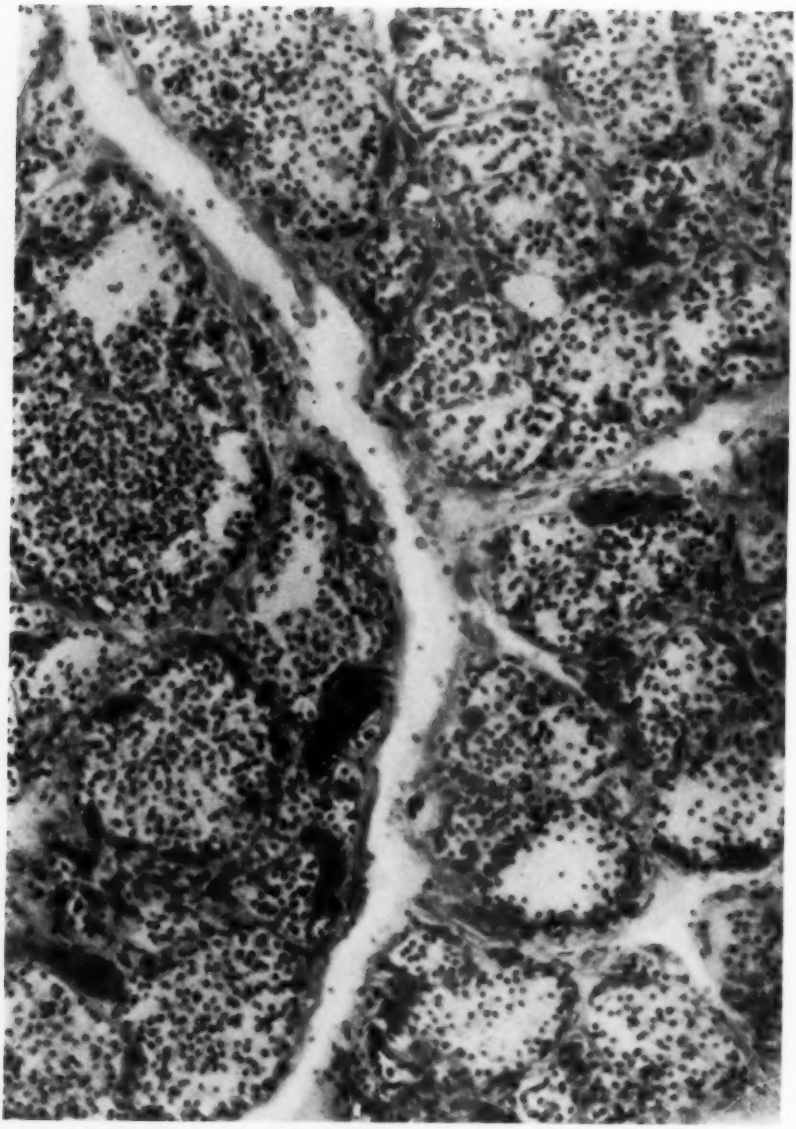

FIG. 8.—Thyroid gland, Case V.

FIG. 9.—Thyroid gland, Case VIII.

spleen and liver. The cicatrices were interpreted as due to repair following necrosis of tubules. The outstanding lesion was the acute severe tubular degeneration.

CASE V.—L. L., aged two years (Hospital No. 80943) was taken ill with coryza, rhinitis and fever and one week later edema of the eyelids developed. He did not appear seriously ill, and played about the house as usual, but as albumin was found in the urine, the patient was brought to the hospital.

Examination revealed generalized edema with a considerable amount of free fluid in the abdominal cavity. The outstanding feature in this case was the extreme edema which, in spite of treatment, varied considerably in degree and in distribution. On one occasion the eyes were completely closed and a few days later the edema disappeared from the face and the scrotum and penis became edematous. During the course in the hospital, various therapeutic measures were instituted: (1) Sodium bicarbonate; (2) calcium chlorid; (3) urea; (4) transfusion; (5) abdominal paracentesis; (6) low-protein salt-free diet; (7) high-protein diet; (8) the antra were opened and drained. These measures were ineffective and three months after admission many petechial lesions appeared, the respiration became rapid and labored and death ensued two hours after a generalized convulsion. During this period of illness the blood pressure was not raised and there were no evidences of increased cerebral pressure. The urinary output was apparently not diminished.

Laboratory Data. Urine: Specific gravity, 1030; 7 gm. of albumin per liter; a few hyalin and granular casts; a few leukocytes; no red blood cells. *Plasma protein*, 5.34 per cent. Antra, cultures staphylococcus albus. *Blood pressure*, 104/50, 95/65, 100/70.

Summary (by Dr. Blackfan before the autopsy). The onset with rhinitis, coryza and fever, evidently from an acute infection is not commonly found in acute tubular nephritis. Nevertheless, the clinical course and laboratory data were consistent with the disease. On these grounds it would seem probable that the histologic changes would be in the uriniferous tubules.

Autopsy (A-25-90) (nineteen and a half hours postmortem). There was marked generalized edema. The peritoneal cavity contained about 3 liters of cloudy liquid with flakes of fibrin; each pleural cavity contained 1½ liters of similar fibrin-specked liquid. The pericardial cavity contained 500 cc. of turbid liquid. Peritoneal and pleural surfaces were injected and fibrin covered, smears from the peritoneal exudate contained Gram-positive diplococci and Gram-negative bacilli. The immediate cause of death was presumably acute peritonitis and pleuritis.

The *heart* weighed 50 gm. and was essentially normal.

Lungs. The left weighed 80 gm., the right 108 gm. The picture was that of fibrinous pleurisy, congestion and edema, with acute alveolar emphysema. The bronchi were free from exudate.

Spleen. The spleen weighed 40 gm. and showed the expected changes of acute peritonitis.

The pancreas showed marked edema of the connective-tissue structures.

The *gastrointestinal tract* showed no lesions in gross.

The *liver* weighed 780 gm. It was very firm (in contrast to other tissues), smooth, finely-mottled deep red and yellow. On section it yielded much blood, and its firmness was probably due to engorgement. Microscopically, extreme engorgement was the outstanding feature. There were a few minute necroses, especially about the central (hepatic) veins and rarely a small fibrin thrombus in a sinusoid. The liver cells in general were small, granular and free from vacuolization. They were reduced in size, often rounded in shape, occasionally stained deep red with pyknotic nuclei.

The *adrenal glands* showed considerable lipoid vacuolization.

The *thyroid gland* and organs of the neck were apparently normal. Microscopically, the thyroid proved to be remarkable for its extraordinary injection of the capillaries, complete absence of colloid and the small size and desquamation of the epithelial cells. A few follicles contained lightly staining colloid. The epithelial cells were small with prominent normal-appearing nuclei, no mitoses. There was marked edema of all the connective-tissue structure.

The *brain* weighed 1100 gm. It was very soft, and there was evidence of marked edema throughout. Microscopically, no cellular reaction was found.

The *Kidneys*. The left weighed 110 gm., the right 108 gm. They were enlarged, yellowish in color, mottled with red, soft and succulent. On section the cortex and interpyramidal regions seemed swollen, the medullary rays were unusually conspicuous because of the opaque-yellowish color with deeply congested bloodvessels. The cortex was flecked with minute opaque-yellowish areas. The pelves and ureters were normal. Microscopically, the outstanding feature was the severe and extensive degeneration of the epithelium of the convoluted and ascending Henle's tubules. The tubules were dilated, filled with granular débris and circular reticulum and granular and hyalin casts. The epithelium was swollen and finely granular or narrowed to a mere fringe. Swollen cells appeared to be discharging their cytoplasm in bud and stream-like processes into the lumina. Very few tubules, however, contained necrotic cells, and these only in isolated instances. No complete destruction of tubules was found. There was a marked basal fat vacuolization of the epithelial cells in many proximal and distal convoluted and ascending Henle tubules. Most of the glomeruli were normal with moderately injected capillaries. Numerous ones, however, showed some blocking of capillaries by polymorphonuclear leukocytes and swollen endothelial cells, not greater, however, than that which accompanies many infectious diseases. There were no cicatrices and the picture was that of recent injury with no possibility of estimating the duration of the injury to the tubular epithelium.

The middle ears were normal. The antra of Highmore contained a thin reddish liquid. Cultures from the right yield staphylococcus, from the left a Gram-negative bacillus.

Case VI.—W. L., aged two years (Hospital No. 92574). Following an illness of two days with fever, vomiting, coryza and cough, edema of the legs was noticed. The patient played around the house, apparently as well as usual, until a week later, when the abdomen became noticeably enlarged and generalized edema developed. He was brought to the hospital because of the edema which had been present for one month. The parents were quite certain that the urine had not been bloody. *Examination* revealed generalized edema with free fluid in pleural and peritoneal cavities. No primary focus of infection was found. He did not appear acutely ill on admission. On the eighth day after admission, the temperature rose gradually, he became worse and died four days later with evidences of pneumonia, empyema, peritonitis and meningitis. The blood culture showed pneumococcus.

Laboratory Data. Urine: Specific gravity, 1025; trace of albumin; few hyalin and granular casts; a few leukocytes; on the first day erythrocytes were found by none thereafter. *Blood:* White blood cells, 163,000; 74 per cent polymorphonuclears. *Plasma protein*, 4.18; N.P.N., 26.7. *Blood culture* and *peritoneal fluid*, pneumococcus.

Summary (by Dr. Blackfan before the autopsy). The onset with signs of an acute infection was followed in two days by edema of the legs. One week later generalized edema and ascites developed. The patient died five weeks after the onset with a widespread terminal infection. The onset and clinical course even are not typical of acute tubular nephritis. On the

other hand, the generalized edema, and terminal infection and the laboratory data, except for the presence of a few red blood cells during the first few days in the hospital are consistent with acute tubular nephritis (N.P.N., 26.7 mg.; plasma protein, 4.18 per cent; blood pressure, 90 mm.). It would be most surprising if the histologic examination showed degenerative changes in the tubules without as well, changes in the other parts of the renal units.

Autopsy (A-26-57) (two hours postmortem). The immediate cause of death was acute fibrinopurulent peritonitis, pleuritis (bilateral) due to the pneumococcus. There was generalized edema. The peritoneal cavity contained about 200 cc. of turbid fibrin-flecked liquid. Each pleural cavity contained about 200 cc. of similar liquid.

The *heart* weighed 42 gm. There was slight edema of the interstitial tissue.

Lungs. The left weighed 67 gm., the right 95 gm. The pleural surfaces were in part covered with a nonadherent fibrinous exudate. The lungs in gross and microscopically showed evidence only of moderate atelectasis in portions. The bronchi and alveoli were free from exudate.

Spleen. Weight, 34 gm. It showed no relevant changes.

Pancreas. Normal.

The Gastrointestinal Tract. Normal.

The *liver* weighed 400 gm. Its surface was covered with fibrinous exudate. Its gross appearance was not remarkable. Microscopically, the parenchyma was essentially negative though the liver cells in central halves of the lobules were reduced in size and occasionally round in shape with discontinuity. Occasional cells lining sinusoids were swollen and vacuolated; there was much granular débris between liver columns and sinusoids, probably an indication of edema.

Adrenals. Microscopically, there was marked engorgement with blood, but cortex and medulla were normal.

The Brain. It was soft and microscopically the cortex showed moderate vacuolization and dilatation of perivascular spaces probably due to edema. The meninges were injected but were free from exudate.

The Kidneys. The left weighed 44 gm., the right 48 gm. They were light brown in color, and slightly soft, but not remarkable in appearance. Pelves and ureters were normal.

Microscopically, the prominent feature was the uniform and marked changes in the tubules, though these were less striking (severe) than in any of the preceding cases. The epithelium of all tubules was affected. That of the convoluted and ascending Henle tubules was unusually swollen and finely granular with only rare cells showing pyknotic nuclei. Very rarely an isolated cell of these tubules was densely stained with eosin and shrunken, the nucleus pyknotic. None of the tubules showed extensive necrosis. All contained granular débris and circular reticulum and some contain hyalin casts, which were numerous in the collecting tubules. The descending tubules of Henle were dilated, filled with granular débris and the cells were reduced to flat platelike objects, the nuclei appeared normal. In the upper portions of these tubules the cytoplasm was more nearly normal in amount and frequently contained coarse, brown, granular pigment. The proximal convoluted tubules contained a moderate amount of fat in small globules which stained deeply with Scharlach R. Numerous glomeruli showed minute droplets in the endothelium. This fat was isotrophic.

The *glomeruli* were with rare exceptions completely normal. The exceptions showed moderate swelling of the endothelium of the capillaries and hence contained less blood. Also an occasional glomerulus containing coarse strands of fibrin in the capillaries. This kidney contained no cicatrices like those of the preceding cases.

The middle ears, frontal and sphenoidal sinuses were normal.

CASE VII.—T. F., aged three years (history lost). *Laboratory data: Urine:* Specific gravity, 1025; marked trace of albumin; hyalin and granular casts; no erythrocytes. Phenolsulphonephthalein, 45 per cent. *Blood:* White blood cells, 25,000 per. com.; polymorphonuclears, 70 per cent; plasma protein, 4.2 per cent; N.P.N., 40 mg. per cent. *Blood pressure:* 100/60.

Summary (by Dr. Blackfan before autopsy). The insidious onset with the characteristic urinary and blood data and the terminal infection suggested that the histologic changes would be degenerative lesions in the tubules, without glomerular lesions.

Autopsy (A-25-88) (one and a half hours postmortem). The immediate cause of death was a generalized fibrinopurulent peritonitis. There was a generalized edema, much thin puriform liquid in the abdominal cavity and a few cubic centimeters of turbid, yellowish liquid in each pleural cavity.

The *heart* weighed 80 gm. The gross and microscopic appearance were normal.

Lungs. The left weighed 88 gm., the right 104 gm. Both were edematous. Microscopically, there was an early bronchitis, peribronchitis and pneumonitis.

Spleen. Weight, 90 gm. It showed no relevant changes.

Liver. Weighed 620 gm. It was somewhat enlarged. The color was mottled red and yellow in areas of lobular dimensions. Microscopically, there was very marked engorgement of the sinusoids with blood. The sinuses contained numerous mononuclear phagocytes and occasional polymorphonuclear leukocytes, and the endothelium was separated from the liver columns by empty spaces interpreted as evidence of edema. The liver cells contain small vacuoles (fat). Occasional ones are deeply stained with eosin. All seemed reduced in size.

Pancreas. Normal.

Gastrointestinal Tract. Normal except for the acute peritonitis.

The *adrenal glands* were markedly engorged. The glomerular zone showed very little lipoid vacuolization. In the fascicular zone were numerous small necroses, usually with disappearance of the adrenal cells and replacement by mononuclear phagocytes and polymorphonuclear leukocytes.

The Brain. There was slight edema.

Kidneys. The left weighed 90 gm., the right 86 gm. They were enlarged, deep red with a very fine pale mottling. The pelves and ureters were normal.

Microscopically, the outstanding feature was the severe and extensive degeneration of the convoluted and ascending Henle tubules. These tubules were universally affected, the least degree being swelling and increased granularity of the cells accompanied by a fine fat vacuolization. (This fat stained red with Scharlach R.) Very few cells contained hyalin droplets. Greater degree of injury was shown by reduction in size of the cells and the presence of densely staining acidophilic masses in the cytoplasm. A few tubules are completely necrotic, with lumina filled with globular hyaline masses. There were numerous mitotic figures in the tubules with this massive hyalin degeneration of the cells and in such instances the picture was reminiscent of that of corrosive sublimate poisoning. The most marked lesions were in the convoluted tubules, blood corpuscles filled occasional convoluted tubules, the others were filled with granular débris, circular reticulum or rarely hyalin casts. The latter were in practically every collecting tubule. The glomeruli were practically normal, a rare one contained a few polymorphonuclear leukocytes and clumps of fused red blood corpuscles. The interstitial tissue was free from wandering cells. There were no cicatrices. The condition of these kidneys may be expressed as that of severe acute tubular degeneration singularly uncomplicated by other lesions.

The middle ears and accessory respiratory sinuses of the skull were normal.

CASE VIII.—V. C., aged twenty-two months (Infants' Hospital No. 92574). With the exception of having had measles when eight months of age, had been regarded as a normal baby until she was fourteen months of age. Then there followed a series of episodes which are of interest. At fourteen months an attack of vomiting which continued for a few days. One week later, the eyelids were swollen. When sixteen months of age puffiness of the eyelids was again observed. Each time the edema lasted only a few days. From then until twenty-one months of age she continued in good health. Three weeks before admission the eyelids again became swollen, this was followed by enlargement of the abdomen. Albumin in large amounts was found in the urine. No blood or red cells were present.

Examination showed generalized soft, pitting edema with free fluid in the peritoneal cavity. No focus of infection was found. She appeared acutely ill. Edema rapidly increased as shown by a gain of 3 pounds in six days.

The patient became extremely drowsy and after four days of fever (105° F.) died.

Laboratory Data. Urine: Specific gravity, 1025; marked trace of albumin; many hyalin casts; no erythrocytes.

Blood. White blood cells, 19,000 per c.cm.; polymorphonuclears, 54 per cent; plasma protein, 3.2 per cent; N.P.N., 44 mg. per cent.

Blood Cultures. Pneumococcus (700 colonies per cubic centimeter).

Blood pressure steadily increased in six days from 120/100 to 170/105 mm. just before death.

Summary (by Dr. Blackfan before the autopsy). It is possible that the edema of the eyelids which occurred first when the child was fourteen months of age, indicated the onset of the disease; that it recurred when she was sixteen months of age and again when she was twenty-one months of age with a terminal pneumococcus septicemia one month later. The clinical course, physical findings and termination are characteristic of acute tubular nephritis as was the plasma protein and the urinary findings. The one outstanding feature which was difficult of explanation in this type of nephritis was the blood pressure. We have never seen hypertension of this degree (170 mm.) in this form of nephritis and so reasoned that this was of the mixed type (glomerulotubular nephritis).

Autopsy (A-29-19) (thirteen and a half hours postmortem). The immediate cause of death was a fibropurulent peritonitis which followed a pneumococcus septicemia. There was generalized edema. The peritoneal cavity contained approximately 500 cc. of pale milky liquid with much pale yellowish fibrin; smears showed Gram-negative bacilli and Gram-positive diplococci identified respectively as the Colon bacillus and Streptococcus viridans. Each pleural cavity contained approximately 200 cc. of exudate similar to that in the abdominal cavity.

The *heart* weighed 62 gm. and was normal.

Lungs. The left weighed 94 gm., the right 118 gm. The pleural surfaces of both were injected and covered with a thin layer of fibrin. They were both congested, with some alveolar collapse.

Spleen. Weighed 50 gm. It showed no relevant changes.

Pancreas. There was marked edema and diffuse infiltration with moderate numbers of lymphoid cells.

The Gastrointestinal Tract. Normal.

Liver. Weighed 600 gm. The gross appearance was not remarkable, though somewhat paler than normal. Microscopically, there was no evidence of the usual type of fat vacuolization. The central halves of most

lobules showed lighter-stained liver cells reduced in size and often rounded in shape with a peculiar mottling. These cells with high power proved to be very finely vacuolated; the mottling was due to deeply basic-stained (hematoxylin) bodies arranged peripherally in the cells. These bodies are of irregular shapes though often circular or ovoid and 1 to 3 microns in diameter. They probably represent an early effect of cell degeneration. There were a few minute focal necroses scattered throughout the sections without reference to anatomical structures.

Adrenal Glands. Were congested with markedly diminished lipoid.

The *thymus* was small. Microscopically, it showed marked atrophy.

Thyroid gland was apparently normal in gross. Microscopically, it presented the same extraordinary appearances of the thyroid gland of Case V. There was complete absence of normal colloid. Most of the alveoli were collapsed, contained many desquamated clearly stained thyroid cells and a small amount of granular material. The capillaries are enormously engorged, tortuous and projected deeply into the alveoli where these were not collapsed; by their prominence they obscured the architecture of the gland. The thyroid epithelium was atrophic, the cytoplasm scanty, finely granular with uncertain outlines. Many nuclei were pyknotic.

Brain. Weighed 1168 gm. There was moderate edema. Microscopically, no cellular lesions were found. There was marked vacuolization of the cortex and basal nuclei and great dilatation of perivascular spaces in the cortex, basal ganglia and fiber tracts which were interpreted as evidences of edema.

Kidneys. The left weighed 73 gm., the right 65 gm. They were smooth, everted slightly from the capsules when incised. The cortices were pale, uniformly yellowish in color. The pyramids, pelves and ureters were normal.

Microscopically, the glomeruli were normal, all showed patent capillaries with a moderate injection with blood. The capsular spaces containing small amounts of fine granular precipitate. The prominent feature was the uniform change in the tubules comparable in severity to Case VI. The convoluted tubules were dilated and filled with granular precipitate and circular reticulum. The epithelial cells were granular, swollen in some instances, in others reduced in size with shaggy free borders. The nuclei stained normally and there was no evidence of actual necrosis of cell. The ascending tubules of Henle's loops showed similar granular degenerative change. Casts were very rare; a few of the hyalin type were found in Henle tubules. Scharlach R stains showed a surprisingly large amount of fat, very uniformly distributed in the convoluted tubules. The droplets were of small size basally situated, and only a rare anisotropic droplet could be found by examination with polarized light.

This kidney contained no cicatrices. No necrosis of tubular epithelium could be found and the histologic appearances were those of a mild process comparable to the type of renal lesions found incidentally so frequently in the routine study of tissues from individuals who died of infectious diseases.

Discussion. *The Kidney.* The kidneys of these 8 children without much possibility for doubt all exhibited the effects of the same disease, characterized by degenerative changes in the epithelium of the convoluted tubules. The mildest recognizable injury was comparable to that usually called cloudy swelling and evidenced by increased affinity for acid dyes and swollen and granular cytoplasm (Fig. 1) (Fahr's first stage), a condition which we have seen produced by prolonged experimental acidosis. (See Seegal below.)

Severer grades were indicated by the presence of hyalin or colloid droplets in the cells (Fig. 2) (Fahr's second stage) or even complete necrosis of all the cells in segments or the whole of tubules (Fahr's third stage). In the severest lesions the presence in the cells of densely stained hyalin material recalled the effect of corrosive sublimate poisoning (Figs. 4 and 6).

The kidneys of Cases I, II, III and IV contained small cicatrices which were without legitimate question the late or end result of complete necrosis of tubules and consequent elimination of glomeruli. In Case III the kidneys (Figs. 3, 4 and 5) showed all stages in sequence from necrosis through cellular infiltration to fibrosis. Also, the distribution and small size of these scars could only be explained by this interpretation. The presence of cicatrices in each instance conformed to a history of at least two remissions in the signs and symptoms of renal disease.

The lesions of the tubular epithelium found at death in each instance may be regarded as the effects of the disease covering the period of illness before death, that is, the last exacerbation or in Cases V, VI and VII of the entire comparatively brief duration of the disease. In every instance, however, we are warranted in believing that the tubular lesions represented the effects of an attack or exacerbation lasting from a few weeks to several months. In no instance was there cellular infiltration of the interstitial tissue of the kidneys except immediately adjacent to necrotic tubular epithelium.

From the above facts one important conclusion may be made: That whatever degree of injury may have existed in the kidney at any one period, the effect is not cumulative. With the exception of complete necrosis of large portions of tubules repair is probably completely accomplished during remissions, while there is histologic proof of replacement of individual necrotic cells by mitotic division of adjacent cells during exacerbations (Figs. 5, 6 and 7). Whether the tubular degeneration of this disease can end in a notably scarred or "contracted" kidney is open to question. Theoretically, on the basis of the cicatrices which we have found and explained as the result of repair following necrosis of tubules, a contracted and insufficient kidney should be a possible outcome.

We must, however, consider whether the lesions found at death were due to terminal events or whether the tubular epithelium throughout each exacerbation was injured to a degree morphologically demonstrable. This is a difficult and perhaps impossible question to answer without biopsy material. The continuous albuminuria and presence of cells and casts in the urine during the attacks or exacerbations support the belief that the tubules are the seat of demonstrable injury. The explanation of the histogenesis of some urinary casts advanced by Jackson[2] necessitates a degree of injury comparable to those we have found at autopsies in the milder degrees

of injury in this series of 8 cases. Incidentally, our histologic studies of this series corroborate the findings of Jackson in regard to the direct derivation from renal epithelium of the material from which certain types of casts are formed.

There is also experimental evidence for the long continuance of injury of the tubular epithelium in the work of Seegal,[3] who showed that in long maintained acidosis in rabbits and dogs produced by the continued administration of tenth-normal hydrochloric acid or of ammonium chlorid (periods up to one year) casts and albumin appeared in the urine throughout the experimental period. She found in the kidneys removed surgically or upon sacrifice of the animals acute degeneration of the epithelium of the convoluted tubules with pyknosis of occasional nuclei and regeneration in cases of longest duration. While the continuous presence of damaged though viable epithelium seems to be the more probable state of affairs in the kidneys of this type of nephritis, routine experiences in the correlation of clinical histories and postmortem material prove the frequent production of similar tubular lesions of even greater severity in a very few days in numerous types of severe infections and toxic diseases in children. Hence the histology of the kidneys gives no clue to the duration of the disease in tubular nephritis unless there are present the cicatrices of lesions of earlier date. The facts force us to seriously consider the possibility of a long-sustained (chronic?) lesion of cells morphologically in a state of acute injury.

The infections which terminate this disease must modify the pathologic histology in the direction of severity. In Case IV the terminal streptococcus infection accompanied by multiple thromboses in lungs and spleen was undoubtedly responsible for the glomerular thromboses. In other cases of the series the slight glomerular lesions could be accounted for as secondary to severe tubular degeneration. In Cases VI and VII, the only ones in which pneumococcus infections were prominent, the renal lesions were least severe.

In but 2 cases, Case III (Fig. 3) and Case VIII, was the quantity of fat a conspicuous feature in the tubular epithelium. In no instance was the fat doubly refractive, though in casts *in situ* in the kidney of Case III fatty acid crystals and doubly refractive lipoid globules were found. The failure to find doubly refractive lipoid in the kidneys from individuals who showed it in the urine during life agrees with the 2 cases studied postmortem which Eckstein[4] reported. The case terminated with pneumococcus peritonitis and glomerulonephritis; the other was a case of tuberculosis with amyloidosis. Doubly refractive lipoids were present in the urines of both. None could be demonstrated in the kidneys after death.

The Thyroid. The thyroid glands of Cases V and VIII (Figs. 8 and 9) are of interest. The changes described, absence of colloid,

atrophy and desquamation of epithelial cells and extreme vascular engorgement may be interpreted as exhaustion effects following excessive functional performance. They demand further study when opportunity offers.

Depletion of colloid and epithelial desquamation occurs in many infectious diseases, and, according to Wegelin,[4] particularly in scarlet fever, smallpox and diphtheria, but also in measles, typhus, pneumonia, epidemic and tuberculous meningitis, tetanus, acute peritonitis and progressive wound infections. Most of these conditions are frequently accompanied by degeneration of the convoluted tubules of the kidneys, yet our own studies show that even in some of the above where severe tubular lesions have been found the thyroid has been normal. In our Warsaw series of typhus autopsies no notable instance of colloid depletion was found in the thyroid. A review of the material shows a slight change in a small number of cases.

In infants and children a review of 77 postmortems revealed 7 instances of notable colloid depletion so that the thyroid appearances recalled or approximated those of Cases V and VII. Two of these were in children who died of milk-borne *streptococcus epidemicus* septicemia; both showed streptococci and thrombi in the glomeruli as well as marked tubular degeneration in the kidneys. Three instances were in infants who died of acute nutritional disturbance with persistent vomiting and dehydration; 1 showed normal kidneys, 1 cloudy swelling of the convoluted tubules and 1 with a severe grade of degeneration of the tubular epithelium. One case was that of an infant, aged thirteen months, with acrodynia, terminating with thrush, bronchitis, peribronchitis and pneumonia. The kidneys showed glomerulonephritis and severe tubular degeneration. One case was that of a boy, aged seven years, who died of fat embolism following an operation for fixation of a tuberculous hip. The kidneys showed cloudy swelling only. In no instance, however, was the thyroid completely depleted of colloid nor were the engorgement and desquamation pronounced.

Eight cases of glomerulonephritis, 2 of long duration, 1 terminating with pneumonia and empyema show normal thyroids with no trace of colloid depletion, engorgement or epithelial desquamation. It would occupy too much space to review the histories and postmortems of the cases with severe infectious processes where the thyroid was normal and kidneys showed tubular degeneration. Our opinions are: (1) That thyroid depletion of the character described occurs independently of the nature of the infecting microorganism; (2) that it is always associated with degeneration of the convoluted tubules; (3) that it may not be found though both infections and tubular degeneration are found; (4) that in typical glomerular nephritis with edema, albuminuria and severe secondary tubular lesions it is characteristically absent; and (5) that it is prob-

ably dependent upon grave metabolic disturbance, presumably often the result of infections of unknown etiology as in the acute nutritional disturbances of infants and in so-called nephrosis. Another approach to the consideration of the thyroid change is suggested by the reports of tubular degeneration accompanied by fat in the epithelial cells and sometimes by cellular infiltration of interstitial tissue and tubules in the kidneys after extirpation of the thyroid gland in carnivora. Wegelin[6] gives a brief review of the subject. We have consulted the original articles upon which he based his review with the exception of one inaccessible at present, that of Rosenblatt.[7]

Blum[8] used dogs, and after thyroid extirpation found regularly degeneration of the epithelium of the convoluted tubules and in long survivals infiltration of the interstitial tissues with round cells, thickening of glomerular capsule and frequently hemorrhages into the parenchyma. He also described toxic fatty degeneration of the liver cells.

Bensen[9] and Kishi[10] used cats and dogs for their experiments and reported substantially the same results as Blum, including the fatty degeneration of renal tubules. Hagenbach[11] mentions only very briefly the fatty degeneration of the convoluted tubules in cats after thyroid extirpation. He also found degeneration of liver cells as described by Blum.

The Liver. The livers of these cases are worthy of special consideration. Unfortunately, owing to restrictions, no weights were obtained in 2 and no histologic material in 1. Four of the series showed marked increase in weight, in 2 instances almost double normal, and in 2 the weight was normal for the age. Where the weight was increased, histologic examination shows that it was due to extraordinary and uniform engorgement of the sinusoids. Without exception the parenchyma cells of these livers were reduced in size; in most instances this was quite marked in the central halves of the lobules, while in other instances many of the liver cells were rounded in outline, giving the effect of discontinuity of columns. Other changes common to the series were those interpreted as due to minor degrees of cellular injury, increased acidophilic stain, fine vacuolization and the presence of a peculiar basic staining reticulum. All of the livers showed considerable granular débris between the liver columns and sinusoids which, together with peripheral vacuolization cells in many instances seemed to warrant the diagnosis of edema. In 2 of the livers there were striking effects unquestionably due to the terminal infections, inasmuch as there were numerous minute thrombi in the sinusoids. In view of the recent work by Thomas, Schlegel and Andrews,[12] by Welker, Andrews and Thomas,[13] and by Andrews, Thomas and Welker,[14] the histologic changes in our series deserves more than casual attention. These workers in the experimental production of uremia by

injections of hypertonic salt solution noticed profound pathologic changes in the liver cells, and were able by immunologic methods to demonstrate the presence of liver protein in the urine. We have already mentioned the association of liver-cell lesions with tubular lesions in the kidney following experimental extirpation of the thyroid gland in cats and dogs.

The same type of discussion that we have applied to the kidney lesions apply, of course, to the liver, and one may well ask what would a biopsy of the liver have shown during life in any one of these cases, for here again routine correlation of clinical histories and postmortem studies gives every reason to believe that any of the changes we have found in the liver may be produced in a very few days as a consequence of infections of one sort or another.

Conclusion. We believe that the 8 cases here presented, because of the clinical and pathologic features common to them all, are representative of a disease entity in childhood. This belief implies a common etiology or pathogenesis for the series.

The pathology of the kidneys affords no premises for the explanation of the important physiologic disturbances of the disease and, therefore, we do not believe that the primary effect of the etiologic agent is upon the kidneys or that the important manifestations of the disease are consequences of injury specific to the kidneys.

The histologically demonstrable damage to the kidneys was found in the tubules. The glomeruli showed only lesions accountable for either by the terminal infection or severe degeneration of the tubules of the same units. In general the glomeruli were without lesions.

Conclusion regarding the rôle of the thyroid in this disease is not possible. The thyroid lesion is probably a manifestation of functional exhaustion and, therefore, probably is neither cause nor direct consequence of the kidney damage.

The pathology of the liver, slight atrophy and degeneration of the hepatic cells, may also be interpreted as effects of overtaxed functional activity consequent to the loss of blood proteins.

While offering no substitute we believe that any name implying a renal origin such as nephrosis or tubular nephritis is not appropriate to this disease.

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TRANSFUSION OF BLOOD IN BRIGHT'S DISEASE.*

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Transfusions of blood are not resorted to very frequently in the treatment of Bright's disease. Hesitation concerning their use arises largely from impressions and is frequently not based upon an analysis of actual observations. Current objections to the use of transfusions in nephritis may be formulated as follows:

1. Blood transfusions may elevate blood pressure and change a comparatively harmless hypertension into one of alarming proportions.

2. There is a feeling among many clinicians that transfusions may, in some manner, produce toxic materials in the blood and tissues, which a damaged kidney cannot eliminate.

3. Transfusions may aggravate an existing renal lesion and thus cause progressive pathologic changes in the kidney and accentuate a renal insufficiency.

Indications for transfusions of blood in Bright's disease, which we propose to analyze, may be summarized as follows:

1. As an aid in treating the uremia attendant upon renal insufficiency.

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2. As a relief for severe anemia.

3. As a means of combating edema by raising the osmotic pressure within the circulation through an increase of the proteins of the blood.

In the past eleven years, we have had many transfusions carried out on patients suffering from Bright's disease. All of them are not reported here, but only a few are mentioned that will serve to illustrate the validity of the indications and contraindications for transfusions in Bright's disease. Some of these cases were transfused by the syringe method; the majority received blood by the direct method of Unger, and most of these transfusions were carried out by Lester and Jonas Unger whose great skill and generous efforts are appreciated by all who know their work at first hand.

The Effect of Transfusions of Blood Upon Arterial Pressure. Our experience has been that transfusions up to 1000 cc. do not increase the blood pressure, no matter how high the arterial tension may be. This is in accord with the findings of Eyster and Middleton[1] who demonstrated that in cases of pernicious anemia after transfusion equivalent to 1 to 1.5 per cent of the recipient's body weight, there was only a slight transitory rise in the systolic, diastolic and venous pressures. Table I illustrates the effect of transfusion on a hypertensive individual, moribund because of renal insufficiency brought on by a secondary contracted kidney. This case is noteworthy because the blood was given very slowly by the syringe method. No changes in the levels of blood pressure occurred as the result of the transfusion.

TABLE I.—EFFECT OF TRANSFUSION UPON BLOOD PRESSURE.

Time, P.M.	Blood pressure.		Remarks.
	Syst.	Diast.	
12.05	225	148	
12.08	220	148	100 cc. blood injected.
12.25	225	150	200 cc. blood injected.
12.36	220	143	300 cc. blood injected.
12.45	220	145	400 cc. blood injected. Transfusion terminated.
7.15	215	140	

January 28, 1919. H. L., male, aged twenty-one years, suffering from severe uremia brought on through renal insufficiency caused by secondary contracted kidney. The patient received 400 cc. of blood given slowly by the syringe method. There was no rise in either the systolic or diastolic pressure.

In Table II another instance of transfusion in a hypertensive individual is given. The procedure here consisted in giving 1000 cc. of blood rapidly, that is within seven minutes, by the Unger method. The blood pressure in this patient showed no increase. It is worth noting that the effect of the nervous strain incident to the preparation for transfusion did cause a very definite rise in the systolic

pressure (from 162 to 228). However, the transfusion itself did not bring about any increase of the arterial tension. It is very significant that a nervous strain can result in a rise of 66 points in systolic blood pressure while a transfusion of 1000 cc. of blood within seven minutes does not have an appreciable effect on the arterial tension. The observation, as given in Table II, shows very clearly that great care must be exercised in interpreting the cause for changes in blood pressure.

TABLE II.—THE EFFECT OF TRANSFUSION UPON BLOOD PRESSURE.

Time, P.M.	Blood pressure.		Pulse.	Remarks.
	Syst.	Diast.		
2.35	162	118	84	Lying down; preliminary to transfusion.
2.42	228	118	84	Preparing for transfusion.
2.45	204	108	90	
2.46	202	116	84	Needle inserted into vein.
2.48	228	122	84	300 cc. blood injected.
2.50	226	124	72	500 cc. blood injected.
2.51	228	122	72	700 cc. blood injected.
2.52	224	120	84	850 cc. blood injected.
2.53	220	116	78	1000 cc. blood injected; transfusion terminated.
2.57	226	124	84	Talking about transfusion.
2.59	220	122	84	
3.01	212	116	84	
3.07	220	116	84	

February 28, 1930. H. C., male, aged sixty-three years, suffering from secondary contracted kidney complicated by secondary anemia, renal insufficiency and hypertension; gout, diabetes mellitus and angina pectoris were also present. The nervous strain incident to the anticipation of the transfusion resulted in a distinct rise in blood pressure. The transfusion of 1000 cc. given rapidly by the direct method did not influence the level of the blood pressure or the pulse rate appreciably. When the apprehension concerning the transfusion was allayed, this patient's blood pressure promptly returned to its habitual level of systolic 160, diastolic 120.

A third case that may be cited, because of his very high diastolic pressure, is that of a young man, aged twenty-nine years, whose blood pressure persistently remained at a level of about 230 systolic and 160 diastolic. In addition, there was some renal insufficiency as shown by a urea N of about 50 mg. per 100 cc. of blood; there was a persistent albuminuria, and there was a secondary anemia with a hemoglobin of about 50 per cent. Because of the desperate situation of this patient, it was deemed advisable to attempt a transfusion. This was carried out and 500 cc. of blood were given by Unger's method. This did not bring about any appreciable change in the level of the blood pressure either during the transfusion or subsequently. The blood pressure was determined during the transfusion at intervals corresponding to the injection of 40 cc. of blood for each reading. A blood pressure of systolic 230, diastolic 160 at the beginning of the operation remained unchanged until 400 cc. had been

given; during the injection of the last 100 cc. the blood pressure was systolic 230, diastolic 156.

Theoretically it might be argued that transfusion of blood must raise blood pressure by increasing the blood volume. In actual practice, we have found that this is not the case. There must be compensatory factors to nullify this possible effect. Evidently the nervous control of the heart musculature, the larger bloodvessels and the arterioles is so adjusted that the blood pressure is maintained at a given height regardless of the volume or character of the blood within the limits demanded by the transfusion of 1000 cc. of blood. From the well-known tendency to hypertension in cases of polycythemia vera, it may be assumed that a certain limit cannot be exceeded.

It may be concluded, therefore, that transfusions of blood in Bright's disease have no effect upon the blood pressure, no matter what the initial level of arterial tension may be. This is of considerable importance in Bright's disease as many of the cases in which the indications for transfusion are particularly urgent, may be subject to a marked degree of hypertension.

The Effect of Transfusion of Blood Upon the Kidney. I. *In Patients Without Bright's Disease.* The transfusion of blood is a comparatively safe procedure and is hardly ever associated with fatal complications. Bernheim[2] reported 800 transfusions, for various conditions, in which there were four deaths brought on by hemolysis. In these operations, performed thirteen years ago or more, the preparatory steps for grouping and compatibility were evidently not carried out as well as they are today. Ottenberg[3] refers to anuria after transfusion as an exceedingly rare occurrence. Blain[4] calls attention to the favorable results obtained in 3000 transfusions. Brines[5] notes the very low incidence of serious reactions during or following transfusions; in his series of 4000 transfusions there were two fatalities and several severe nonfatal reactions. Brines[5] believes that such reactions are more common when nephritis is present. He cites three instances among 4000 transfusions in which oliguria or anuria occurred with an elevation of the blood urea. There is, however, no proof that nephritis antedated or was the particular cause of these sequelæ. His reference to Blain[4] in support of his contention is somewhat puzzling since Blain,[4] in his article, does not mention nephritis. Individual instances of anuria following blood transfusions are reported by Goormaghtigh,[6] Curtis,[7] Bancroft,[8] Oliensis[9] and Witts.[10] In all of these fatal or severe post transfusion reactions, either hemolysis or anaphylactic shock appeared to be the cause for any complicating effect upon the kidney; the anuria, the hemoglobin infarcts of the kidney and the few instances of tubular nephritis may be explained in this way.

The Effect of Transfusion of Blood Upon the Kidney. II. *In Bright's Disease.* Transfusions of blood have been carried out in

cases of Bright's disease by a number of clinicians without apparently damaging the kidney in any way. Bell[11] reported an instance of relief of anuria in an eclamptic primipara, aged twenty-four years; after a transfusion of 500 cc. of blood the patient became rational in three hours, within sixteen hours 50 ounces of urine were eliminated and in the succeeding twenty-four hours 71 ounces of urine were voided. Ramsay[12] found improvement after transfusion in a case of nephritis with anuria. Ottenberg[3] carried out a large number of transfusions on individuals with diseased kidneys and several individuals with one kidney, none of whom showed any untoward effects. Wearn, Warren and Ames[13] transfused 4 cases of secondary anemia accompanying advanced nephritis without experiencing any difficulties. Martin[14] believes that transfusion overcame oliguria in a seven-year-old boy with edema and albuminuric retinitis. Epstein,[15] and later Clausen,[16] performed transfusions in cases of nephrosis (parenchymatous nephritis) and did not note any unfavorable results upon the kidneys. Burmeister,[17] by alternating venesection and transfusion of normal blood in dogs poisoned by bichlorid of mercury, found less extensive changes in the kidneys as compared to control animals in which this form of treatment was not carried out. Bowers and Trattner[18] report marked improvement in a boy, aged eleven years, with very severe acute nephritis (blood urea as high as 319 mg. per 100 cc.) after decapsulation of the kidneys followed by 4 venesections and transfusions of blood. It is exceedingly difficult to estimate the value of any therapeutic measure in the treatment of acute nephritis as such patients have a very distinct tendency to recover from their acute—so-called uremic or preuremic—symptoms. However, it is permissible to conclude from the findings of Bowers and Trattner[18] that transfusions do not damage the kidney in the severest possible type of acute nephritis.

In the present series of transfusions of blood in Bright's disease there were only 2 cases (Tables III and IV) in which the introduction of blood could possibly be thought to have had an ill effect. The transfusion of blood in the patient whose data are given in Table III was carried out at a time when there was a terminal progressive oliguria which, apparently, was not influenced either favorably or unfavorably by the transfusion. The case shown in Table IV was the victim of a hemoglobinuria; this, apparently, did not influence the existing oliguria to any great extent; however, the blood urea N increased enormously; no evident symptoms resulted from this extremely high concentration of urea in the blood. This patient's death was inevitable and it was neither hastened nor retarded, in our opinion, by the transfusion.

From the literature and our own experience, it would appear that anuria following transfusion may occur. This anuria is not particularly frequent in cases of Bright's disease; in fact, a cessation

of the formation of urine has not been noted in this condition. On the contrary, it is stated by several authors that in Bright's disease the elimination of urine is not interfered with but may even be

TABLE III.—NEGATIVE EFFECT OF TRANSFUSION IN TERMINAL UREMIA.

Date. 1919.	24-hour vol. urine, cc.	Blood urea N., mg. per 100 cc.	Remarks.
Jan. 1–10	2070–4010	37	
11–20	1170–2940	70	
21	2010		
22	2160		
23	1260	136	
24	930		
25	1275	156	
26	1140		
27	600		
28	1125	160	Blood transfusion, 400 cc.
29	1280		
30	330		
31	450		
Feb. 1	750		
2	180	..	Died.

H. L., male, aged twenty-one years, secondary contracted kidney with terminal uremia. Transfusion of blood by the syringe method in this case did not serve to ward off uremia. The oliguria which may, on casual observation, be thought to have been brought about by the transfusion evidently was definitely making itself felt for about four weeks previously; this is shown, not only by the diminishing quantities of urine, but also by the progressive increase in the blood urea N, indicating that the compensatory polyuria was failing.

TABLE IV.—NEGATIVE EFFECT OF TRANSFUSION IN TERMINAL UREMIA.

Date. 1924.	24-hour vol. urine, cc.	Blood urea N., mg. per 100 cc.	Remarks.
Oct. 12	..	152	Retention uremia present; transfusion (Unger method) two weeks ago
14	300		
15	680	..	Blood transfusion, 700 cc.
16	540		
17	90	380	
18	200		
19	190	357	
20	220	345	
23	..	..	Died.

P. D., male, aged forty years, secondary contracted kidney and terminal uremia. In this case, oliguria, following the transfusion of 700 cc. of blood by the direct method, was present before the transfusion was resorted to; hence, transfusion cannot be regarded as bringing about the diminished amount of urine any more than it could in the case charted in Table III. The marked increase in the blood urea N following the transfusion is noteworthy. This was evidently brought on by destruction of red cells since there was a distinct hemoglobinuria associated with the rise in the blood urea N. No evident symptoms resulted from this extremely high concentration of urea in the blood.

stimulated by the transfusion of blood. Diminished kidney activity after transfusion appears to occur only as the result of various factors induced by incompatibility of the blood of the donor with that of the recipient. Anaphylactic phenomena and hemoglobinemia may be cited as the most prominent causes. The effect of these would seem to be the same in normal persons as in those suffering with Bright's disease. The existence of Bright's disease, therefore, should not be regarded as a contraindication to transfusions of blood.

The Relation of Transfusion of Blood to Uremia in Bright's Disease. Transfusions of blood do not alleviate the symptoms of uremia brought on by renal insufficiency, nor do they, apparently, postpone the onset of uremia, when they are resorted to some months previous to the fatal onset brought on by the retention of urinary excretory products. This has been the experience of many clinicians and is ours as well; this is illustrated in Tables III, IV, V and VIII. The procedure of first bleeding patients who are suffering with retention uremia, and subsequently transfusing them with a corresponding amount of blood, has proved itself of no value in a considerable number of cases and this, we believe, is the universal experience. There may be one exception to this statement as illustrated by the experience of Burmeister[17] on dogs. As previously mentioned, he found less extensive changes in the kidneys of dogs poisoned by bichlorid of mercury, when alternating venesection and transfusion of normal blood was resorted to.

There is an idea among many clinicians that transfusions of blood may be harmful in those cases of Bright's disease in which the blood urea N is elevated. Boyd[19] reports transfusions in two such instances and finds that the patients were benefited and not harmed. We have never hesitated to carry out transfusions on patients who gave evidences of nitrogen retention in the blood. The results, with the exception of those to be mentioned in the next paragraph, have been uniformly without untoward effects. Records are given in Tables V, VI and VII of patients whose blood urea N was 63, 54 to 61 and 45 to 27 mg. of urea N per 100 cc. of blood, and where the transfusions of blood did not influence the quantity of urea in the circulation. It is our opinion that when the blood urea is very high, in such instances as given in Table III, the effect of transfusion on the blood chemistry is negligible.

Occasionally, with the production of hemoglobinemia, that is, a destruction of the red blood cells, the blood urea may increase enormously. We have seen this occur on two occasions, one of which is illustrated in Table IV. In this patient, the blood urea nitrogen rose from 152 to 380 mg. per 100 cc. after transfusion. This reaction, presumably, is due to some deficiency in the adaption of the blood of the donor to the recipient. As previously mentioned, it is of rare occurrence and as the methods of matching

bloods are perfected, it grows even less frequent now than in the past. It is satisfactory to know that these huge increments of blood urea are apparently not productive of symptoms; they seem to have no effect upon the patient nor do they aggravate the uremic signs. This is in accord with the growing belief that urea in itself is not the toxic substance responsible for uremia.

It may be concluded that transfusions of blood are not contraindicated in uremic states but that no aid for the alleviation of this condition can be expected from them.

The Value of Transfusions of Blood in Treating the Secondary Anemia Occurring in Bright's Disease. Secondary anemia is the invariable accompaniment of severe renal insufficiency as shown by Brown and Roth,[20] by Ashe[21] and by Wilbur and Brown.[22] This condition may assume such severity as to invalid the patient and, what is equally important, it may be the sole cause for weakness and ineffectiveness of the sufferer from Bright's disease. Such patients derive great benefit from the administration of blood by transfusion. We have used this form of treatment extensively and have never found it to produce any harmful results. The patient treated in Table V showed a moderate anemia at the time of his first trans-

TABLE V.—NEGATIVE EFFECT OF TRANSFUSION IN TERMINAL UREMIA WITH ALLEVIATION OF ANEMIA.

Date.	Hb., per cent.	R.B.C., millions.	Blood urea N., mg. per 100 cc.	Blood transfusion, cc.	Remarks.
1925.					
May 27	70	4.992	45		
1926.					
Mar. 10	65	3.200	63		
24	..	..	..	850	
29	78	4.480			
Sept. 13	50	2.240	63		
15	..	..	..	700	
21	72	3.944	..	700	
28	58	3.096	77	..	First signs of uremia.
Oct. 7	..	..	85	..	Uremia.
Nov. 1	21	1.260	259	..	Uremia.
2	..	..	..	..	Died.

A. S., male, aged thirty-seven years, secondary contracted kidney, renal insufficiency, hypertension. Transfusions of blood served to alleviate the anemia; they produced no untoward symptoms; they did not prevent a fatal termination from retention uremia, though they doubtlessly added much to the happiness and the effectiveness of the last eight months of the patient's life.

fusion. His anemia and the symptoms dependent upon it were relieved. Six months later it was found necessary to repeat the procedure since, as is almost invariably the case with a marked renal insufficiency, the anemia was progressive. However, the life of this individual was made worth while for a period of about six months before the terminal uremia manifested itself. A similar

finding is shown in the case the details of which are given in Table VI. The additional point which may be stressed here is that in this individual the anemia had progressed so far (hemoglobin 39 per cent, red blood cells 1,355,000) that a fatal termination would

TABLE VI.—BENEFICIAL EFFECT OF TRANSFUSION ON ANEMIA.

Date.	Hb., per cent.	R.B.C., millions.	Blood urea N., mg. per 100 cc.	Blood transfusion, cc.
1926.				
Nov. 18	80	3.900	16	
1927.				
Jan. 18	74	3.632	33	
Mar. 12	77	3.264	19	
Oct. 12	60	3.808		
1928.				
Mar. 6	56	3.456	22	
May 5	59	3.032	29	
Dec. 8	76	3.400	43	
1929.				
Nov. 2	43	2.600	54	
11	39	1.355		
13	..	..	..	800
14	51	3.056		
15	..	..	61	
18	..	..	..	800
19	58	3.912		
22	63	3.400	59	
24	..	..	..	900
25	74	4.688		
Dec. 2	74	4.936		
10	70	4.064	53	
30	70	4.552		
1930.				
Jan. 13	53	3.688	51	
21	52	3.152		
30	56	4.032	55	
Feb. 12	52	3.096	49	
25	42	2.632		
28	..	..	..	1000
Mar. 1	63	2.208		
5	52	3.904		

H. C., male, aged sixty-three years, chronic diffuse nephritis, gout, diabetes mellitus, angina pectoris. For two years a mounting nitrogen retention and an increasing anemia. Transfusion produces no increase in blood urea and benefits the anemia and its associated symptoms. It is obviously impractical in this case to remedy the very threatening anemia (hemoglobin 39 per cent, red blood cells 1,355,000) by high-protein feeding since the blood urea is at a high level and retention uremia would ensue; transfusion of blood is the only solution for temporary relief. The transfusions held the progressive anemia in check for about three months, when it was found necessary to repeat them.

have ensued through the anemia alone unless the transfusions had been carried out. The first series of transfusions in this case held the progressive anemia in check for periods of about three months, when it was found necessary to repeat them. This patient, after

having been threatened with the fatal complication of progressive anemia, was able to carry on his business affairs, to take vacations in the South and to start on a trip to Europe during the ensuing six months.

TABLE VII.—BENEFICIAL EFFECT OF TRANSFUSION ON ANEMIA.

Date.	Hb., per cent.	R.B.C., millions.	Blood urea N, mg. per 100 cc.	Blood transfusion, cc.	Remarks.
1929.					
May 17	69	4.232	38	..	
24	54	3.110	..	..	
29	..	..	27	1000	
31	60	3.300	..	..	
June 3	60	3.488	..	..	
5	62	3.768	43	750	Diet throughout contained 40 to 60 gm. protein a day.
10	70	3.750	..	..	
13	80	4.360	45	750	
Sept. 11	72	4.840	25	..	
Oct. 15	86	5.144	23	..	
Dec. 10	85	4.536	22	..	
1930.					
Jan. 31	85	4.960	18	..	
April 25	85	5.232	25	..	

F. F., male, aged forty-three years, secondary contracted kidney with a moderate impairment of renal function. The progress of the anemia was checked by several transfusions; subsequently this patient did very well with a protein intake of 40 to 60 gm. a day. This case serves to illustrate that an anemia occurring in some forms of Bright's disease may be rapidly, safely and more or less permanently remedied by blood transfusions. When the impairment of renal function is marked (see Tables V, VI) the anemia recurs, whereas if the kidney eliminates the urinary excretory products satisfactorily, the hemoglobin and red blood cells, as in this case, can be maintained at a normal level for an indefinite period.

The above 2 cases give the result of transfusions carried out in the later stages of Bright's disease. When they are resorted to earlier in the condition (Table VII), the results are much more satisfactory. Under these circumstances, the anemia is much more rapidly remedied than it can possibly be by diet and medication, and if the diet is sufficiently high in protein, the blood may be maintained in a normal condition more or less permanently. All of this was accomplished in the case shown in Table VII. This patient had been rendered anemic, weak and an invalid through protein-food restrictions imposed upon him because of albuminuria, hypertension and renal insufficiency. The anemia at the beginning of the observation, it may be noted, was a progressive one, the hemoglobin dropping from 69 to 54 per cent and the red cells changing from 4,232,000 to 3,110,000 within a week. Following the transfusions, not only was the blood brought to an approximately normal level but the progress of the anemia was completely checked. This is in marked contrast to the 2 previous cases (Tables V and VI) where renal insufficiency was very much more marked. It may be that

transfusions of blood given early in chronic diffuse glomerular nephritis, when anemia and the accumulation of nonprotein nitrogen in the blood are just beginning, will prevent the progressive destruction of red cells and furnish a stimulus for the maintenance of a normal level of hemoglobin and erythrocytes. This is a problem that should be investigated very much more thoroughly but it certainly presents possibilities exceedingly worthy of consideration. The patient described in Table VII, six months after the series of transfusions, gradually resumed his arduous duties as a priest, felt strong and well and maintained his hemoglobin and red blood cells at a normal level without difficulty. In any event, the early use of transfusions can do no harm and may be productive of excellent results. It is worth mentioning that in the case, charted in Table VII, the albuminuric retinitis existing at the beginning of the observation, improved to a remarkable degree. Dr. Martin Cohen, who watched the eyes of this patient, said that he had scarcely ever seen a comparable degree of improvement in the retinitis of Bright's disease.

Secondary anemia occurring in the course of Bright's disease may thus be regarded as a very definite indication for the use of transfusions. This is so because the secondary anemia in itself may produce invalidism and because such a secondary anemia cannot be remedied by dietary measures within the limitations necessitated by the coëxisting renal insufficiency. In the later stages of Bright's disease, transfusions of blood may be regarded as a palliative measure only, since they relieve the secondary anemia temporarily, but not for very long. If transfusions are used at an earlier period, when renal insufficiency is first beginning to manifest itself and the secondary anemia is not very marked, there may be a chance to remedy the secondary anemia, more or less permanently, and to check its progressive character. We would, therefore, advocate the use of transfusions of blood for secondary anemia occurring in Bright's disease, whether the anemia be mild or severe, whether it occurs early or late in the course of the nephritis. On the whole, the earlier in the course of the disease that transfusions are resorted to, the more satisfactory will be the results obtained.

The Use of Transfusions of Blood for the Elimination of Edema in Bright's Disease. This has been advocated by Epstein[15] in cases of nephrosis. Clausen[16] resorted to transfusions in parenchymatous nephritis with the idea of remedying the secondary anemia and increasing the blood protein. The theory that edema in Bright's disease is largely due to the diminished osmotic pressure of the blood, accompanying the lowering of the blood proteins, is gaining ground and it would seem rational to suppose that transfusions would be of aid in this connection. The only case in which we have given the procedure a thorough trial (Table VIII) did not show any improvement in the anasarca when the hemoglobin and red blood cells were

elevated by means of transfusions from hemoglobin 52 per cent and red blood cells 2,810,000 to 83 per cent hemoglobin and 4,000,000 red blood cells. The subsequent use of transfusions in attempting to maintain the blood at a high level had no further effect. Although the efforts to control edema by transfusion in this case were unsuccessful, we believe that this method of treatment warrants further investigation.

TABLE VIII.—BENEFICIAL EFFECT OF TRANSFUSION ON ANEMIA, BUT WITHOUT EFFECT ON EDEMA.

Date.	Hb., per cent.	R.B.C., millions.	Blood urea N, mg. per 100 cc.	Blood transfusion, cc.	Remarks.
1929.					
Mar. 4	52	2.810	21	..	
13	..	..	..	750	
19	50	2.704	..	..	
20	..	..	..	750	
23	77	3.700	..	..	
30	72	3.680	..	..	There was subcutaneous edema and ascites constantly present; these were not influenced by level of hemoglobin and red blood cells.
April 6	83	4.000	19	..	
15	70	3.720	..	..	
29	72	4.150	32	..	
May 6	51	2.960	..	..	
15	..	..	..	1000	
Aug. 14	..	..	..	700	
Sept. 11	60	4.000	25	..	
28	60	3.700	..	..	
30	..	..	..	500	
Oct. 20	55	2.920	52	..	
28	..	..	69	500	
31	..	..	..	500	
Nov. 6	..	..	..	500	
11	68	3.360	..	..	
16	..	..	..	..	Died.

J. B., female, aged thirty-two years, chronic diffuse nephritis of seventeen months' known duration; there was a marked degree of anasarca. Transfusions of blood, though they served to improve the blood, raising the hemoglobin from 52 to 83 per cent and the red blood cells from 2,810,000 to 4,000,000 per c.mm., did not result in a diminution of the fluid in the subcutaneous tissues or the body cavities. The repeated transfusions of blood did not increase the blood urea content nor did they have an untoward effect of any sort; they probably served to maintain life for a considerable period, as this patient could not overcome her anorexia and ate scarcely any food.

Summary and Conclusions. In cases of Bright's disease treated by other clinics or physicians we have noted that transfusions of blood have been resorted to without untoward results; however, many clinicians fear the use of blood transfusions in nephritic patients because of damage that might be induced in the kidneys. This fear seems not to be the result of actual experience but to be based merely on certain preconceived impressions. From our own findings and those in the literature cited above, we believe that anuria and other complications of transfusion are rare and, further-

more, are not more common in cases of Bright's disease than in other conditions. Several instances of nephritis and anuria are quoted, in which transfusions were followed by distinct improvement in the activity of the kidneys; in our experience, transfusions of blood have no distinct diuretic effect and we believe that when an increased output of urine resulted it was due to the recovery of the kidney function independently of the added blood.

Transfusions of blood in Bright's disease do not raise the blood pressure, do not injure the kidneys, and neither relieve nor aggravate uremic symptoms; they furnish the most suitable means of treating the secondary anemia accompanying marked renal insufficiency; in one case of anasarca complicating a chronic diffuse nephritis neither the subcutaneous edema nor the ascites were relieved by raising the hemoglobin and red blood cells to normal levels by means of repeated transfusions. Further studies should be carried out on the last problem before a definite answer can be formulated in regard to it.

The principal indication for the transfusions of blood in Bright's disease is in the relief of the progressive secondary anemia accompanying impairment of renal function. In such cases it is impossible to remedy the condition by a high-protein diet as retention uremia would be a sequel. Transfusions will ameliorate a serious condition for a long period when the kidneys are moderately involved, for a short time only if the renal parenchyma is largely destroyed. Several successive transfusions are, as a rule, necessary to restore the hemoglobin and red blood cells to an approximately normal level. The procedure may have to be repeated at intervals if the secondary anemia recurs.

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THE ETIOLOGY OF ERYTHEMA NODOSUM IN CHILDREN.

Its Relation to Early Tuberculous Infection.

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Erythema nodosum is seen frequently by the dermatologist and internist. The surgeon sees the condition usually because it may be mistaken at first sight for a suppurative skin condition. Because of its frequent association with diseases of the nose and throat it is occasionally observed by rhinolaryngologists. Because of its rare occurrence in the first decade of life it is not often seen in pediatric practice. During the past four years we have observed 8 cases in the Stanford Children's Clinic, an incidence of about 1 case in 900 children, or 0.11 per cent.

Sutton[1] defines erythema nodosum as "an inflammatory disease of the skin which is accompanied by a variable degree of constitutional disturbance, and is characterized by an eruption consisting of a few or several rounded or oval, painful nodules which persist for two or three weeks and then disappear spontaneously." These nodules are usually more numerous over the tibiæ, but may appear on the surfaces of the upper extremities as well. The condition is observed more frequently in females, and the usual occurrence is from ten to thirty years of age.

The histologic picture shows foci of cellular infiltration in the corium, and especially in the subcutaneous fat. Inconstant infiltrates are seen in other layers of the corium. The infiltrates are chiefly perivascular and around the glands, consisting of round cells, some multinuclear granulation tissue cells and polymorphonuclear leukocytes. Fibrinous exudates may occur in the subcutaneous fat and occasionally small hemorrhages are also found here. The endothelium in the small vessels is frequently swollen and shows large nuclei.

Mackenzie's work in 1886,[2] which associated rheumatism and erythema nodosum, was not challenged until Lendon,[3] in 1905, suggested a different etiology. He believed this condition to be mildly infectious and a definite clinical entity. He described prodromal, eruptive and convalescent stages. Phlyctenular conjunctivitis was the only prodromal sign which he regarded as pathognomonic.

Symes[4] supported Lendon's views and also believed that erythema nodosum strongly predisposed the individual to tuberculosis.

Ernberg[5] made an elaborate study in support of the theory that erythema nodosum is due to a transient hypersensitiveness to tuberculin in individuals recently infected with tuberculosis. He called attention to the similarity of the process to an artificially elicited tuberculin reaction in a tuberculous individual. The agreement is shown clinically by a similar local reaction, general reaction and focal reaction, and the two are very similar histologically.

Comby,[6] in a study based on 172 personally observed cases, regarded it as an acute febrile disease resembling more an eruptive than an ordinary skin disease. He believed that an almost extinct tuberculosis might become active in its presence because the tuberculous child is particularly susceptible to all infections. He thought that this was the extent of the connection between tuberculosis and erythema nodosum.

Faerber and Boddin[7] reported 23 cases, in 21 of which the tuberculin reaction was positive. They excluded the possibility of tuberculosis in the other 2 cases. In the 21 children they noticed no unfavorable activating effects on tuberculosis and no progressive tuberculosis followed any of the attacks of erythema nodosum. Nearly all showed heavy hilus shadows by Roentgen ray following the attacks, and several showed definite epituberculous foci near the hilus of the lung.

Robinson[8] reported 3 cases of erythema nodosum in 3 different members of the same family, living in the same house. In 45 cases Feer[9] reported no definite joint involvement or endocarditis in any cases. He collected 749 cases from the literature. Endocarditis was found in only 3, indicating the great improbability of an etiologic association with rheumatic infection. Of 403 cases from the literature tested with tuberculin, 384, or 95.3 per cent, gave positive reactions. Under seven years of age, all of the patients

reacted positively. The reactions were usually very strong, even vesicular or necrotic. Various types of tuberculosis were found in this series, bronchial gland tuberculosis being most common. He did not find that the cases ran a more severe course than the usual juvenile infection.

Arborelius[10] considered the eruption as a nonspecific reaction occurring in various infections, recent tuberculous infection predominating in childhood and youth, other infections of various kinds being the usual cause in older persons. A school endemic of erythema nodosum was reported by Wallgren.[11] The 18 cases all gave a positive Pirquet reaction and occurred in a class of 32 children. A recently admitted child in this class had well-developed pulmonary tuberculosis. After the second month of the first child's attendance in school, 17 children showed signs of the infection, 12 presenting erythema nodosum and 6 fever but no lung symptoms. Two months later 13 showed evidence of pulmonary lymph gland tuberculosis and 4 presented suggestive lesions. Wallgren[12] also reported erythema nodosum occurring during the course of the initial fever in tuberculous infection in children.

The following cases are reported from the Pediatric Service of Stanford Medical School, all of which show an association of erythema nodosum with a tuberculous infection.

Case Reports. Case I.—M. W., a girl aged ten years, entered the children's ward with complaint of tender, reddened, swollen areas over lower legs for one week, and over forearms for one day. The past history and family history gave no significant information. Physical examination showed nothing except many tender, reddened or purplish nodules over the legs and forearms, varying in size from 1 to 2 cm. On the leg they were limited to the anterior aspect, over the tibiæ, and to one over the anteromedial aspect of the right knee. On the forearms they were on both the posterior and anterior surfaces. The admission temperature was 38.6° C. Blood and urine were normal. Intracutaneous tuberculin was strongly positive in all dilutions down to 0.001 mg. In a dosage of 0.01 mg. a tender indurated, reddened nodule was produced, resembling very closely the lesions of erythema nodosum, with a suggestion of vesiculation in the center of the reaction. Roentgenograms of the chest showed a considerable mass of density at the left lung root (Figs. 1 and 2). The patient underwent a normal convalescence, although several additional lesions of erythema nodosum appeared after she was first seen. All lesions gradually faded, and she had no fever except for her first day in the children's ward.

Case II.—E. K., a girl aged three and a half years, was admitted to the children's ward with a complaint of pain in the abdomen and legs, and loss of appetite, for the past four days. The family history was negative. The past history was unimportant except that the child had had uncomplicated measles, beginning eighteen days before her entrance. Physical examination showed a pale and listless child with a temperature of 101° F. The tonsils were large and reddened and the tongue markedly coated. There were many small shotty palpable lymph nodes in the neck. There was paronychia of the right middle finger. There were present over the tibiæ several painful, tender, reddened nodules typical of erythema nodosum.

The tuberculin test was strongly positive. Urine and stool examinations were normal. The white blood cells were 14,750 in number with 66 per cent polymorphonuclears, 28 per cent lymphocytes, 5 per cent large mononuclears, and 1 per cent eosinophils. Roentgenograms of the gastrointestinal tract after a barium meal were negative. Roentgenograms of the chest revealed a mass, probably glands, lying to the right of the midline and extending upward from the hilar region. Hilar shadows on each side were extensive (Figs. 3 and 4). This patient had fever as high as 102° F. during her three-day stay in the hospital. Three days after dismissal her temperature was normal, and the abdominal pain had disappeared. There were still present over the shins the fading lesions of erythema nodosum. The patient did not return to us again.

Case III.—P. G., girl aged three years, reported to the Outpatient Clinic, with complaint of lassitude, nausea, and abdominal pain of one week's duration, and of painful lumps on the legs for one day. The patient had been vaccinated one week previously and had received her third toxin-antitoxin injection against diphtheria on the same day. The family history was entirely negative except for a history of gonorrheal vaginitis in an older sister. Past history was entirely negative. Physical examination revealed a moderately ill child with a temperature of 99° F. rectally and a pulse of 130. There was some mucus discharge from the nose. The tonsils were reddened and showed signs of infection. In the skin over the lower one-half of both tibiæ were several raised, reddened, tender nodules, typical of erythema nodosum. Vaccinia was present over the left deltoid. Blood and urine examinations were negative. Cervical smears were negative for gonococci. The tuberculin test was strongly positive. Roentgenograms of the chest showed markedly increased density and presumably large glands in the left hilus (Fig. 5). The child was entirely well in about one week's time, and the skin lesions had disappeared except for some pigmentation. The vaccinia healed normally.

Case IV.—A. F., a girl aged ten years, entered the children's ward with complaint of reddened, sore areas over the right shin of two weeks' duration, and over left shin, of three days' duration. The child had been going to school and had no other complaints during the two weeks' period. The family history was negative. In the past history there had been evidence of a chronic sinusitis with occasional bronchial spasm (asthma) for the last four years. The tuberculin test was positive four years previously with evidence of moderate inflammation at the lung roots at this time. Examination showed a well-nourished girl with some dental caries. The pharynx was very granular in appearance, with some purulent material on the left posterior wall of the pharynx. There were reddened, tender, indurated areas over both shins, with increase of local temperature over these areas. The blood showed white cells 14,650 in number, with 81 per cent polymorphonuclears, 17 per cent lymphocytes, 1 per cent large mononuclears, and 1 per cent eosinophils. The urine was normal. An intracutaneous tuberculin with a dose of 0.05 mg. was strongly positive. Roentgenograms of the chest showed heavy densities at the right lung root, greatly increased over those showing in previous films. While under observation the patient had no further complaints, no fever, and is entirely well about eight months after being first seen. The skin lesions gradually faded, and disappeared over a further period of two weeks from the first observation.

Case V.—W. G., a boy aged two and a half years, came to the children's ward with complaint of fever, intermittent vomiting, irritability, and loss of weight, all of one month's duration. About three days before the begin-

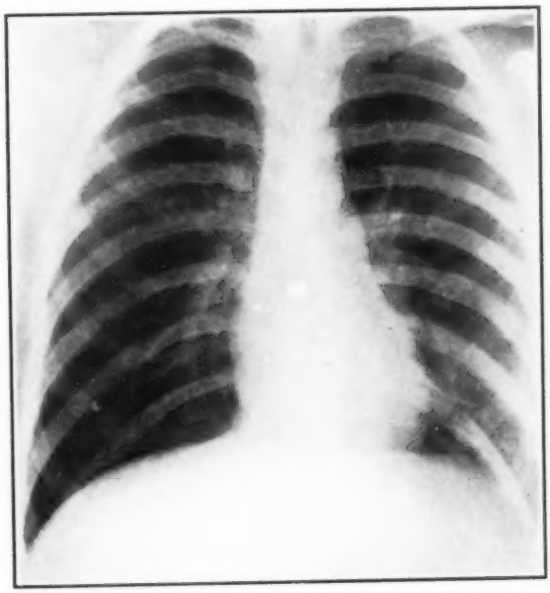

FIG. 1.—Case I. Girl, aged ten years. Roentgenogram of chest, showing probable epituberculous lesion near left hilus.

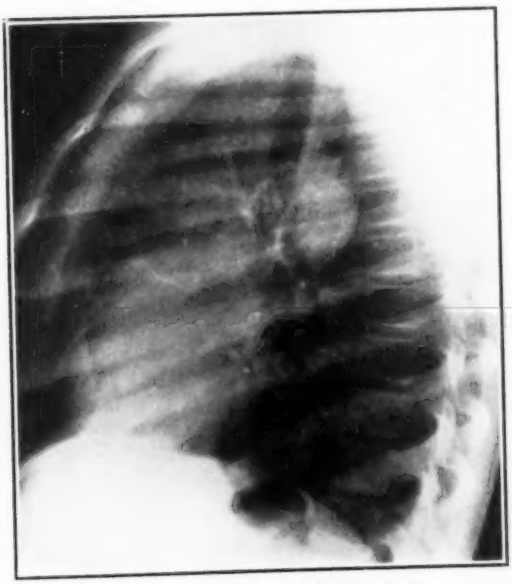

FIG. 2.—Same as Fig. 1, left lateral view.

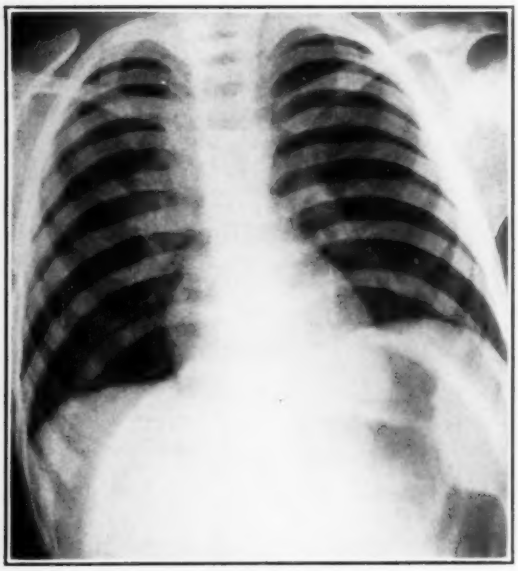

FIG. 3.—Case II. Girl, aged three and a half years. Roentgenogram of chest, showing extensive hilar shadows, and density on right side extending upward from hilar region.

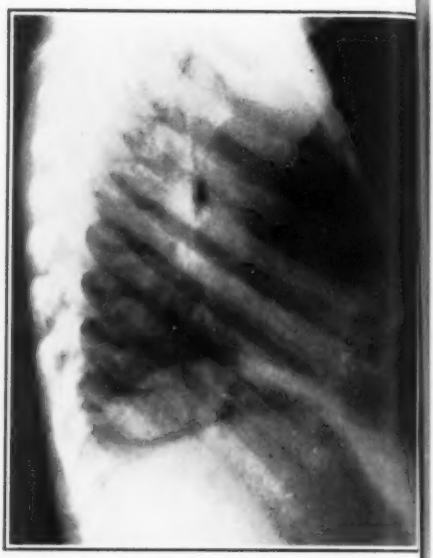

FIG. 4.—Same as Fig. 3, right lateral view.

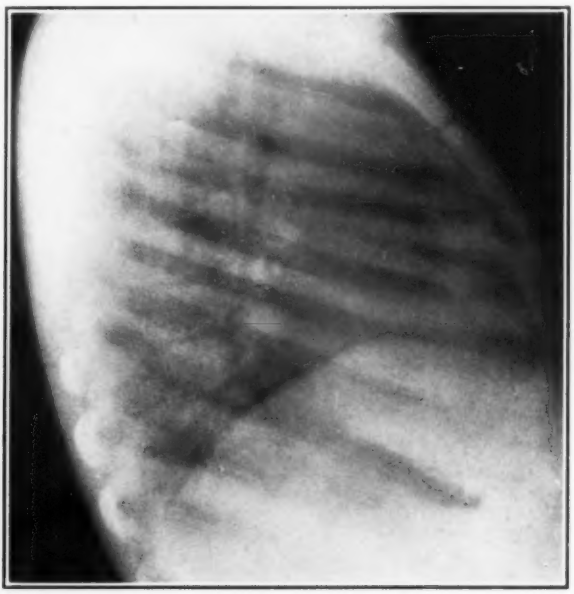

FIG. 5.—Case III. Girl, aged three years. Left lateral view showing density near left hilus.

FIG. 6.—Case V. Boy, aged two and a half years. Roentgenogram of chest showing densities near both hiluses.

FIG. 7.—Same as Fig. 6, right lateral view.

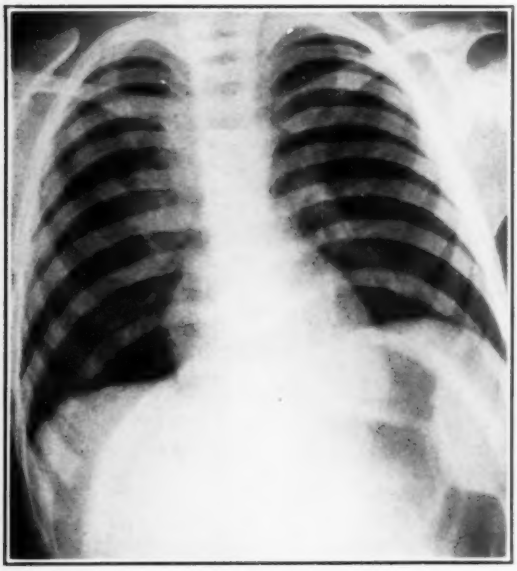

FIG. 3.—Case II. Girl, aged three and a half years. Roentgenogram of chest, showing extensive hilar shadows, and density on right side extending upward from hilar region.

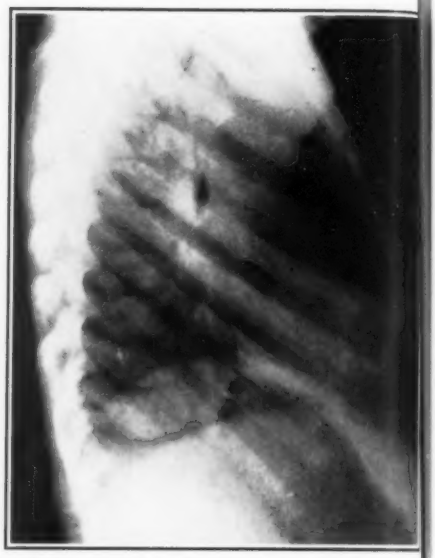

FIG. 4.—Same as Fig. 3, right lateral view.

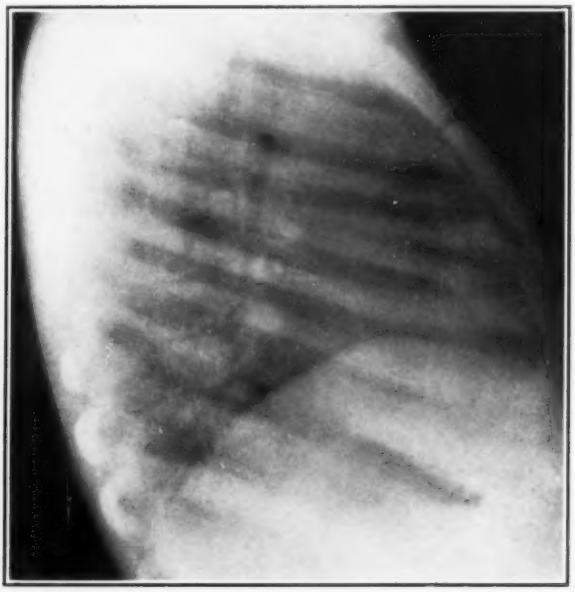

FIG. 5.—Case III. Girl, aged three years. Left lateral view showing density near left hilus.

FIG. 6.—Case V. Boy, aged two and a half years. Roentgenogram of chest showing densities near both hiluses.

FIG. 7.—Same as Fig. 6, right lateral view.

FIG. 8.—Case IX. Boy, aged fourteen years. Roentgenogram of chest, showing heavy hilar shadows and density in the costodiaphragmatic angle on the left side.

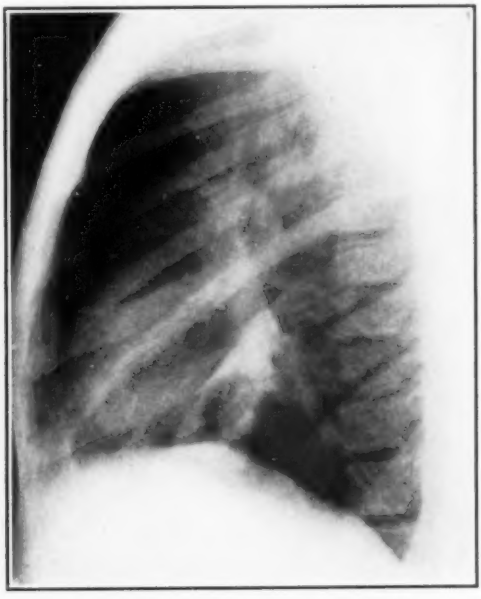

FIG. 9.—Same as Fig. 8, left lateral view.

ning of the present illness, the patient had been dismissed from the hospital following a cough, cold, and diarrhea of about one week's duration. The temperature had been 103° F. on the first day of entry, and had returned to normal the next day. There were no important findings in the physical examination, except that the spleen was barely palpable. The blood count was 4640 white cells, with 69 per cent polymorphonuclears, 16 per cent lymphocytes, 8 per cent large mononuclears, and 7 per cent transitionals. Urinalysis was negative. The tuberculin test was negative. During the patient's infancy there had been frequent attacks of acute otitis media, and two attacks of bronchopneumonia. In the family history there was a note of "miner's consumption" in the father . The temperature during the present illness had ranged from 99° to 103.4° F., being highest in the afternoon. Vomiting had followed almost every feeding, and the child's weight had fallen from 40 pounds to 34½ pounds in the one month. Extreme irritability had been present and he had cried at the slightest provocation. He had been much more drowsy than usual. About ten days before the present entry there had appeared several reddened and tender spots over both shins. Physical examination revealed a pale, apathetic child with a temperature of 101° F. The tonsils were very large and ragged, with moderate injection. There was a blowing systolic murmur over the apex. The spleen was palpable 3 to 4 cm. below the costal margin, the liver 2 to 3 cm. Over both shins were crops of brownish and reddish nodules, firm and slightly tender. Brownish pigmentation suggested other faded areas. The hemoglobin was 66 per cent (Sahli). The white blood cells were 17,550 in number, with 80 per cent polymorphonuclears, 15 per cent lymphocytes, and 5 per cent transitionals. Urinalysis was negative. The tuberculin test was very strongly positive, with marked induration. Roentgenograms of the chest showed dense and extensive hilar shadows (Figs. 6 and 7). Blood cultures were negative. The fever resolved after several days in the hospital. The child was kept in bed for one month at home, the weight was regained, and he made an apparently uneventful recovery.

Case VI.—L. J., a girl aged twelve years, reported to the Outpatient Clinic with complaint of lassitude, fever, and pains in chest, of three days' duration. The father had been actively tuberculous. The child had been a patient in our Clinic for about three years and had reported often for minor ailments and had been treated for a mild chronic sinusitis. Because of her possible contact with tuberculosis she had been tested on three different occasions with 0.1 mg. of tuberculin, always with a negative result. At this visit, which was four months after the last negative test, she was tested with a similar dose and forty-eight hours later the test was strongly positive and there were present several reddened, painful, tender nodules over the shins. The temperature had been 102° F. at home and was 99.2° F. in the Clinic. Otherwise physical examination was negative. The white blood cells were 11,400 in number, with 72 per cent polymorphonuclears, 24 per cent lymphocytes, 2 per cent large mononuclears and 2 per cent transitionals. Roentgenograms of the chest showed enlarged hilar glands. She had no further fever, the erythema nodosum subsided completely in about ten days, and the patient has now been entirely well for two and a half years. About one month after her first positive tuberculin test her father suffered from a pulmonary hemorrhage, his disease progressing rapidly from this point and ending fatally within a year.

Case VII.—I. S., a girl aged nine years, reported to the Outpatient Clinic because of a vaginal discharge of one week's duration. Father was supposedly an asthmatic with a severe cough. Child had been observed in the Clinic since birth for various minor ailments. Because of failure to gain

and of chronic cough in father, tuberculin test was done five months previously to present illness. There was a strongly positive reaction and roentgenograms of the chest revealed marked hilar densities on both sides. Examination at the present time revealed a markedly underweight child. There was slight discharge but marked reddening about the vaginal and urethral orifices. The left inguinal lymph nodes were tender and enlarged with edema in the soft tissue and slight reddening over the swelling. Several typical lesions of erythema nodosum were present below both knees, and one on the lateral side of the left thigh just above the knee. Unfortunately tuberculin and roentgenographic studies were not done at this time. Both vaginal and cervical smears were negative repeatedly for gonococci. The child is well three years later, but is still underweight.

Case VIII.—V. B., a boy aged two and a half years, came to the Children's Clinic with complaint of swollen glands in the neck, of three weeks' duration. The family history was negative. There were no complaints other than of the progressive enlargements of the glands of the neck and of slight fever during this time. The patient had been hospitalized at the San Francisco Hospital early in the illness, where the glands were compressed. The tuberculin test was then negative. Examination revealed a moderately pale child with evident lassitude. The temperature was normal. The tonsils were very large and slightly injected. There was a large mass on the right side of the neck about the size of a lemon, firm and not tender. There was no redness nor fluctuation. There was moderate enlargement of the other cervical lymph nodes. The skin was clear. A tuberculin test was performed and when the patient reported in forty-eight hours for reading, there was a marked positive reaction with extensive reddening and induration. There were many small, reddened, indurated nodules in the skin over the arms, thighs, and legs, chiefly on the extensor surfaces, varying in size from 0.5 to 1.5 cm. in diameter. The mother said that these had appeared the night before. The urine was negative. White blood cells were 16,900 in number, with 54 per cent polymorphonuclears, 42 per cent lymphocytes, 1 per cent transitionals, 2 per cent eosinophils, and 1 per cent basophils. Roentgenograms of the chest were essentially negative. Smears from material aspirated from the gland showed acid-fast bacilli, and a guinea-pig inoculated with material showed tuberculosis one month later. The child remained well for two weeks and then suffered from an attack of measles. The glands had to be incised, and are still draining four months later, although the patient is suffering no constitutional symptoms. A roentgenogram of the chest taken three months after the first film was studied showed definite glandular enlargements in the posterior mediastinum causing compression of the trachea.

Case IX.—D. S., a boy aged fourteen years. This case is from the private records of Dr. Harold K. Faber and Dr. J. G. Bacher, both of whom I wish to thank for permission to include it in this series. The patient was seen by Dr. Faber in consultation with Dr. Bacher, four days after a simple mastoidectomy for acute mastoiditis. Previous to this there had been discharge from the left ear for three weeks. Three months previously patient had complained of night sweats, lassitude, and daily fever of 100° to 101° F., all of which had persisted. Pains in the limbs and joints had followed and roentgenograms of the chest suggested a small effusion on the right side. There had been present over the shins successive crops of reddened, tender nodules for two or three weeks. There was a questionable history of casual exposure to tuberculosis, but not in the home. Examination revealed dullness to percussion at the base of the left lung. In the axilla, on extreme inspiration, pleural friction was heard. The skin was

clear at this time. The tuberculin reaction at forty-eight hours, with a dosage of 0.01 mg., showed an induration of 8 mm. in diameter, with a faint violaceous discoloration around this of an area of 18 mm. by 25 mm. The white blood cells were 16,400 in number, with 75 per cent polymorphonuclears, 23 per cent lymphocytes, and 2 per cent basophils. Roentgenograms of the chest showed density laterally and in the costodiaphragmatic angle (Figs. 8 and 9). These shadows disappeared on subsequent films taken about a month later. Curettings of the mastoid at the time of operation showed granulation tissue in the marrow spaces and in some areas tubercles composed of fibrous tissue cells, some epithelioid cells, and a few multinuclear giant cells. Acid-fast stain failed to reveal any tubercle bacilli. The boy underwent a normal convalescence following the mastoidectomy, all fever disappeared after the fifth day, and he is well fifteen months later.

Discussion. The 8 cases seen in our Clinic represent the total observed over a period of four years. Of the 9 cases in the reported series, 3 occurred in boys, aged two and a half, two and a half and fourteen years, respectively. Six occurred in girls, aged three, three and a half, nine, ten, ten and twelve years, respectively.

In those cases where previous tuberculin tests had been done all were negative except in 2 cases, although at the time of the appearance of the lesions of erythema nodosum, or shortly after, all tuberculin tests were strongly positive with induration, tenderness and erythema which in most cases simulated closely the nodular lesions over the tibiæ. In 1 instance the nodules appeared about twenty-four hours after the introduction of tuberculin into the skin.

In only 2 of the cases in this series was a history of exposure to tuberculosis elicited despite the fact that all skin tests were positive.

The roentgenograms of the chest in those cases in which they were taken demonstrated heavy shadows around the hiluses, and in a majority masses of density that were not nodular in outline, but suggestive of consolidation of adjacent pulmonary tissue such as occur in the typical "epituberculous," or "perifocal" lesion. Histologically it is known that these lesions resemble those of erythema nodosum and the positive tuberculin skin reactions.

In one of the cases there was an active tuberculous lesion of the cervical lymph nodes, and possibly in another case, activity in the mesenteric lymph nodes. In the last case of the series a tuberculous focus was demonstrated in the mastoid. In none of the patients observed later did there ever develop any serious tuberculous disease of the chest, but the usual treatment of juvenile tuberculosis was instituted in all those cases which were observed after the appearance of erythema nodosum. In 4 cases there was associated, in addition to a proved tuberculous infection, in one an asthma and chronic sinusitis, in one a vaginitis, probably nonspecific, in another a vaccinia and in another a convalescence from measles.

Pons[13] observed giant-cell formation in the center of a nodule

of erythema nodosum and Landouzy[14] an acid-fast bacillus in the lumen of a vessel within a nodule. These observations have possibly kept alive the belief shared by some that true erythema nodosum is always related in some way to tuberculosis.

There has accumulated in the literature enough evidence to prove that erythema nodosum may either be caused by or associated with other conditions than tuberculosis. Rosenow[15] has presented evidence to show that the streptococcus is a factor. It has also been reported as associated with smallpox,[16] influenza[17] and other infectious diseases.[10] Possibly in many cases associated conditions influence the allergy, or hypersensitiveness to tuberculin in previously infected tuberculous individuals, so that here tuberculous infection would also be the primary cause. There are also reported cases where sensitiveness to tuberculin has been definitely disproved.[7,17]

It is safe to state, however, that in children by far the largest number of cases of erythema nodosum is associated with tuberculous infection, and that the infection is usually initial and recent. The statement is more true the younger the individual. There is nearly always an associated hypersensitiveness to tuberculin. The etiologic rôle of tuberculosis becomes less constant with increasing age.

In children under twelve years of age the presence of erythema nodosum should be considered as an evidence of a recently acquired tuberculous infection unless there is definite proof to the contrary, and in its presence the treatment of initial infection should be started.

Conclusion. 1. Erythema nodosum may occur in nontuberculous individuals or in those infected with the tubercle bacillus.

2. The great majority of cases of erythema nodosum in children are associated with a tuberculous infection and most of the infections are initial and recent.

3. Most children who have erythema nodosum exhibit marked hypersensitiveness to tuberculin given intracutaneously.

4. There may be associated, in addition to the tuberculous infection, other conditions which possibly influence the hypersensitiveness to tuberculin.

5. In many cases of erythema nodosum in children epituberculous lesions in the pulmonary parenchyma can be demonstrated by roentgenograms of the chest.

6. In the series reported none of the individuals observed was known to develop a very active tuberculous lesion of the lung.

7. The lesions of erythema nodosum, the epituberculous lesions and the positive skin tuberculin reactions are similar histologically.

8. As erythema nodosum is usually associated in children with early tuberculous infections, proper treatment for the latter condition gives a favorable prognosis as far as tuberculosis is concerned.

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ANTISTREPTOCOCCUS SERUM TREATMENT OF PATIENTS WITH RHEUMATIC FEVER.

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In the present stage of the therapy of rheumatic fever, any promising remedial agent deserves serious consideration. Except for the antiarthritic and antipyretic drugs, together with the usual measures of strict hospital routine, we have been without means of influencing the course of this infection. It is true that in certain instances these drugs have been reported to exert a favorable effect upon prolonged conduction time,[1] and that occasionally the symp-

toms of carditis respond in as pleasing a fashion as does arthritis; nevertheless common experience has taught that the salicylate effect usually represents an interlude in the course of a disease which, once established, frequently proceeds relentlessly to the production of serious and often eventually fatal lesions. The appearance of subcutaneous nodules in patients under the full influence of salicylate or neocinchophen has been cited as demonstrating the inability of these drugs to prevent the occurrence of more deeply seated damage concomitantly wrought. The importance of the claims of Small,[2] that the serum developed by him is competent to arrest this damage, can, therefore, scarcely be overestimated; and in view of his results, as well as of the enthusiastic report of Baruffaldi,[3] together with the claims of earlier investigators, it has seemed well worth while to investigate further the effects of antistreptococcus serum upon the course of the disease.

In view of the possibility that many types of streptococci may act in the causation of the disease in subjects peculiarly hypersensitive, it seemed reasonable to attempt to determine whether different antistreptococcus sera might not have similar therapeutic effects.

Commercial antitoxic and antibacterial antiscarlatinal serum prepared by the New York City or State Health Departments was employed as antihemolytic streptococcus serum. Through the kindness of Dr. Small, a quantity of S.C.A. (indifferent streptococcus) serum, both bovine and equine, was made available. The equine serum was in concentrated form. For the production of anti-green-streptococcus serum a strain, V110A, originally isolated from an excised subcutaneous nodule, was chosen. With this organism a heifer was immunized by the intravenous route, first with heat-killed vaccine, eventually with large quantities of living culture. After several months' immunization the animal was bled, and about 3 liters of serum of agglutinin titer approximately 1 to 5000 were obtained. This serum, hereinafter referred to as V110A bovine, was stored in the icebox without preservative.

The intramuscular route of administration was always employed, except in one instance when the serum was given intravenously. Suitable intradermal tests with normal sera were always carried out, and, except in two cases referred to below, no serum to which there was evidence of skin sensitiveness was employed.

The evaluation of the effect upon rheumatic fever of any therapeutic measure is a matter of no mean difficulty. The universal application of salicylate therapy has served in a measure to obscure the really tremendous variability in the course of the disease, particularly with respect to such aspects as fever and arthritis. Reference to the older literature[4] reveals how well this variability was realized before the introduction of antirheumatic drugs. It has been no unusual experience with us to observe marked improvement

in these manifestations, occasionally even complete relief, under expectant therapy alone, within a few days of hospitalization. In the absence of adequately prolonged control periods, such improvement might well have been ascribed to serum therapy, had this been undertaken shortly after the admission of the patient. With regard to severe carditis or to pericarditis, the known tendency of these conditions to pursue more or less self-limited cycles has removed uncertainty to some extent, provided that the treatment has been undertaken sufficiently early in the cycle to warrant the supposition that spontaneous improvement has not been at hand. Even so, however, the uneven course of the disease forbids too dogmatic an interpretation of results.

In this study, emphasis has been laid upon an attempt to secure adequacy of the control period, save only when the condition of the patient has rendered immediate action imperative. In the case of arthritic patients, it seemed desirable to give serum only after several days' observation had apparently established that the disease was running an irregularly continuous course without remissions, or at best with slight and temporary ones; or when, in spite of irregularities in temperature, intensification of the arthritis, with involvement of fresh joints, seemed to indicate the imminence of renewed activity of the infection. Even so, it is with a certain degree of reservation that the occasional improvement of joint symptoms has been attributed to the serum. As regards carditis and pericarditis, the indications have been much clearer; lengthy control periods have usually been precluded, because in each instance the patient has been in the grip of so serious an infection that rapid spontaneous recovery has seemed out of the question. Favorable results observed in this group we have felt might be ascribed largely to the therapy employed, which, let it be noted, was a combination of serum and drug.

The relief only of the major manifestations of rheumatic fever cannot be taken to indicate recovery from the disease, in view of the chronicity of manifestations which may be masked by the use of salicylates. Such items as persisting leukocytosis, subfebrile temperature, failure to gain weight, and variability of the electrocardiogram are now recognized as indicative of persistent infection. No less important, therefore, than adequacy of the preliminary control is minute observation of the patient during the period through which the serum effect may reasonably be expected to persist. This is placed by Small at three weeks or more. It is of course of paramount importance for a proper study that drugs should be withheld during this period. In our study the period of withholding other remedies has only occasionally been so extended, either because of absence of beneficial effects within a few days or because of relapses well before the termination of the prescribed interval. Such relapses, observed not later than two weeks following the treatment, may

reasonably be considered as therapeutic failures regardless of the degree of temporary benefit observed. After all, temporary benefit may usually be rapidly secured with antirheumatic drugs; hence before these can be supplanted by serum, it must be shown that the action of the latter is comparably efficient and reasonably prolonged. With these considerations in mind, we have endeavored to determine as accurately as possible the post-therapeutic course of our patients. The results of the observations have been summarized upon special charts as well as in bedside notes.

To judge critically a single therapeutic agent one should eliminate other favorable influences which arise from hospitalization, adequate nursing, complete rest and proper food; yet these measures are requisite for the patient's welfare. It seems scarcely necessary to emphasize how much more confusion would result if, simultaneously with the serum therapy, were exhibited such drugs as sodium salicylate in arthritis, or bromids or luminal in chorea. Such a study might illustrate still further the efficacy of the drugs, but would be without value with respect to the serum. As far as possible, therefore, we have, except in the case of severely ill patients, abstained from the use of salicylates until satisfied of the failure of the serum. Unfortunately, in a few instances, salicylate was administered at or before the time when the serum effect might have been manifest, and thus the post-serum control period has been inadequate. These few patients, observed in a preliminary study, are included only for the sake of completeness. In the presence of circulatory failure, it has similarly seemed preferable to withhold digitalis insofar as possible. While it is theoretically improbable that this drug would influence an active rheumatic infection, the antipyresis occasionally observed following its administration to patients with congestive failure might confuse the picture were it employed in combination with serum therapy.

Occasionally other irregularities have crept in, as stated in the footnotes to the tables. Attempts at desensitization of two serum allergic patients did not prevent alarming anaphylactoid manifestations after larger doses of serum. Sometimes intradermal tests have been carried out with streptococcal proteins, either during the period of treatment, or shortly before. Although the combined dosage of these proteins never exceeded 0.03 mg., we have subsequently come to realize that this amount is at times sufficient to determine general and focal exacerbations of the disease.

The results are summarized in Tables I to IV, and in illustrative case histories at the end of the paper. In accordance with the advice of Dr. Small, the large doses originally employed were later replaced by smaller ones; consequently it has been necessary to subdivide the tables to follow the alteration of method.

Comment upon these results is interesting. The one patient with chorea to whom the serum was given failed entirely to show evidence

of improvement. A disappointing failure to influence polyarthritis favorably has been encountered, for among 12 patients with this symptom only 3 showed complete and permanent relief; 2 after S.C.A. serum and 1 after antiscarlatinal. Various degrees of improvement which because of their evanescence can only be classed as failures, were noted following all three sera. Surely this result is eloquent. Were salicylate as ineffectual as serum in this condition, its use would long since have been abandoned. Four patients with carditis showed no evidence of even temporary improvement; in 2 of them the disease progressed steadily to death. In Case 4 a severe carditis developed well within a week of the completion of the serum therapy, and shortly thereafter a crop of subcutaneous nodules appeared. When such nodules were present before the institution of serum therapy, their normal involution showed no acceleration. In the case of pericarditis, however, an attitude of complete pessimism seems unwarranted. It is possible that the combination of drug therapy, given because of the serious character of the symptoms, together with the serum was responsible for the favorable results. Such mixed treatment doubtless confuses validity of conclusions, though it may be argued that drugs alone usually exert only a mild influence upon the course of pericarditis. But the prompt and progressive improvement following the combined therapy in Cases 7, 11 and 17 was probably not attributable entirely to the drug. Although the effect of spontaneous improvement might possibly be evoked in Cases 7 and 11, it is unlikely it would apply in Case 17, where treatment was given at the upturn of the cycle. Obviously, results from such small series as the present cannot settle the point, but can merely indicate possibilities which can be affirmed only after extensive and painstaking observation.

Various reactions quite apart from the usual manifestations of serum sickness have been noted, irrespective of the type of serum employed. The most usual occurrence has been a rise in the temperature, occasionally quite abrupt, at an interval of from three to eight hours following injection. The interpretation of the fever curves is not always an easy matter, because of the innate unevenness of their course; in questionable cases one must judge as well as possible by comparison with the control period. Usually, but not always, a coincident tachycardia was noted, and occasionally there occurred a moderate tachypnea. Such febrile reactions were observed in 57 per cent of the patients, more commonly following the first dose of serum, sometimes in connection with all, occasionally with increasing severity as the course of treatment progressed. Arthritic reactions were noted in 53 per cent of the patients in whom arthritis was the predominant manifestation. These appeared within twenty-four hours of the injection, and consisted either in exacerbations in joints already involved, or in spreads to joints previously unaffected. Such reactions have been described by Small,

TABLE I.—RESULTS WITH S.C.A. SERUM.

Case No.	Name.	Age.	Type of disease.	Day.	Length of control period, days.	Dose (A) in cc.	Reactions (B).	Therapeutic effects.	Remarks.
1*	M.S.	39	Arthritis, carditis, pulmonary	30	1	60 (3) Equ.	Moderate temperature and pulse (1, 2, 3)–5 to 10 hrs.; moderate arthritic (1, 2)–24 hrs.; râles increased (1)–24 hrs.; new murmur (1)–24 hrs.	None	Neocinchophen given after 48 hrs.; prompt relief and progressive improvement.
2**	G. H. (C. R.)	7½	Carditis, circulatory failure	7	6	53 (2) Equ.	None	Slight antipyretic; pulmonary signs appeared on day of second treatment	Became steadily worse; required digitalis; neocinchophen given 2 days after completion of treatment, with moderate improvement only; 2 days later large pleural effusion.
3	J. I.	15	Carditis, nodules, circulatory failure	4th yr.	157	20 (3) Equ.	Shock and chill (1)–30 min.; marked temperature and pulse (1)–8 hrs.	None	Eventually died.
4	S. E. (C. R.)	6	Arthritis, carditis	6	3	5 (2) Equ.	Moderate arthritic (1)–24 hrs.; slight temperature and pulse (2)–3 hrs.; marked respiration (2)–7 hrs.; gallop accentuated (1)–24 hrs.	Marked antiarthritic; otherwise none	Four days later relapse with arthritis and carditis; 1 week later nodules.
5†	A. R.	16	Arthritis, carditis	15	3	10 (3) Equ.	Moderate temperature (1)–7 hrs.; severe temperature; moderate pulse and respiration (2, 3)–6 to 7 hrs.; stupor and delirium (1)–7 hrs.; lasted 3 days; ectopic beats (1, 2)–24 hrs.	Marked antiarthritic; marked antipyretic; marked antitoxic and marked anticarditic	During treatment received large doses of neocinchophen; all improvement could be ascribed to this; severe relapse on drug withdrawal 3 weeks later.
6	A. E.	25	Arthritis, pulmonary	34	5	10 (3) Equ.	Moderate temperature (1, 2, 3)–5 to 11 hrs.; marked pulse and respiration (1)–9 hrs.; new pulmonary signs (1)–24 hrs.	Moderate antiarthritic; slight antipyretic; pulmonary condition unaffected.	One week later temperature became higher, pulmonary condition worse, and relapse of arthritis; responded promptly to neocinchophen.

7††	R. M. (C. R.)	18	Arthritis, pericarditis	22	9	10 (3) Equ.	Moderate temperature and pulse (2)–6 to 10 hrs.; slight arthritic (2)–24 hrs.	Marked antipyretic; marked antiarthritic; marked antipericarditic	Severely ill; neocinchophen given for 1 week before treatment without effect and continued in small doses during treatment; pleuritic relapse 2 weeks after treatment; thereafter did well.
8	M. Z.	41	Arthritis	19	6	24 (2) Bov.	Slight arthritic (1)–24 hrs.	Antiarthritic, almost complete; antipyretic complete	Permanent; no drug necessary.
9	C. K. (C. R.)	30	Arthritis	44	5	50 (3) Bov.	Slight temperature (2, 3)–4 to 8 hrs.	Moderate antiarthritic and moderate antipyretic for 24 hrs.	Thereafter severe relapse; neocinchophen given 9 days after completion of treatment; prompt relief.
10	F. P. (C. R.)	33	Arthritis, carditis	17	2	40 (2) Bov.	None	Marked antipyretic; marked antiarthritic; marked anticarditic	After 3 days a pericardial rub appeared for 48 hrs.; no drug necessary.
11‡	M. F. (C. R.)	22	Pericarditis, carditis, arthritis	93	9	50 (3) Bov.	Moderate temperature (1, 2)–3 to 4 hrs.; marked pulse and respiration (1)–3 hrs.; delirium, toxemia, cyanosis (1)–3 hrs.	Marked antipyretic; marked anticarditic; marked antipericarditic; marked antitoxic	Neocinchophen begun on first day of treatment on account of serious condition; no relapse followed drug withdrawal at end of serum course.
12‡‡	J. G.	10	Pericarditis, arthritis	5	1	19 (3) Bov.	Moderate arthritic (1, 2)–24 hrs.	Moderate antipyretic; slight antiarthritic; heart worse	Neocinchophen given 36 hrs. after completion of treatment; prompt but temporary drug effect, with pericarditic and pleuritic relapse after 5 days.
13§	S. R.	7½	Chorea	41	37	27½ (2) Bov.	Slight temperature (1)–8 hrs.; slight pulse (1)–12 hrs.	None	Given 0.01 mg. streptococcus protein i. v. 2 days before beginning treatment.

(A) Figures in parentheses indicate days over which total dosage given was distributed.
(B) Figures in parentheses indicate dose after which reaction occurred. Periods of time following dashes indicate interval elapsing before reaction was noted.
* Insufficient control and observation periods; included only for sake of completeness. Skin tests with 0.03 mg. streptococcus proteins on day following completion of treatment. Not included in Table IV.
** Observation period of only two days because of rapid deterioration.
† Not included in Table IV.
†† Treatment begun on eleventh day of pericarditis.
‡ Admitted with arthritis only; developed pericarditis under observation; treatment begun on fifth day of pericarditis.
‡‡ Insufficient control and observation periods; included only for completeness. Skin tests with 0.03 mg. streptococcus proteins on first day of treatment. Not included in Tables IV, V and VI.
§ Treatment given during a course of immunization with hemolytic streptococcus protein.
C. R.—For case reports see end of paper.

TABLE II.—RESULTS WITH V110A SERUM.

Case No.	Name.	Age.	Type of disease.	Day.	Length of control period, days.	Dose (A) in cc.	Reactions (B).	Therapeutic effects.	Remarks.
14	M. B.	22	Arthritis	7	3	40 (2)	Slight arthritic (1)–24 hrs.	Slight antiarthritic and slight antipyretic, 20 hrs. after first dose.	Thereafter much worse.
15	H. C.	19	Carditis, arthritis, nodules	35	8	40 (2)	Moderate temperature (1, 2)–4 to 8 hrs.; cyanosis and restlessness (1)–12 hrs.	Slight antiarthritic for 4 days; otherwise none	Became progressively worse; fibrillated after 2 weeks; neocinchophen given after 5 days.
16*	J. S.	48	Arthritis	30	1	45 (2)	Moderate temperature and pulse (1)–4 to 8 hrs.; dyspnea and cyanosis (1)–4 hrs.	Antiarthritic, almost complete, for 6 days	No antipyretic effect; after 6 days severe relapse, controlled only by full doses of neocinchophen.
17†	A. P. (C. R.)	8	Pericarditis, pulmonary	18	11	20 (2)	None	Marked antipyretic; cardiac and pulmonary condition improved gradually	Received neocinchophen 2 gm. daily during treatment; 1 week later rub returned for 3 days, then settled down into subacute course.
18	R. F.	33	Arthritis	43	5	47 (3)	Marked arthritic (1, 2, 3)–24 hrs.	Worse	Three days later given neocinchophen with prompt improvement.
19	W. F. (C. R.)	41	Arthritis	26	2	40 (2)	Moderate temperature and pulse (1, 2)–3 to 6 hrs.; slight arthritic (1, 2)–24 hrs.	Marked antipyretic; marked antiarthritic	After four days severe febrile and arthritic relapse, yielding promptly to neocinchophen.
20	I. S.	18	Arthritis, carditis	78	34	50 (3)	Moderate pulse (3)–2½ hrs.	None	After 3 days entered upon a moderately severe cycle of fever and arthritis.

(A) Figures in parentheses indicate days over which total dosage given was distributed.
(B) Figures in parentheses indicate dose after which reaction occurred. Periods of time following dashes indicate interval elapsing before reaction was noted.
* Skin tests with streptococcus proteins on first day of treatment.
† Neocinchophen 2 gm. q.d. during treatment.
C. R.—For case report see end of paper.

TABLE III.—RESULTS WITH SCARLATINAL ANTITOXIN.

Case No.	Name.	Age.	Type of disease.	Day.	Length of control period, days.	Dose (A) in cc.	Reactions (B)	Therapeutic effects.	Remarks.
21*	L. B.	48	Arthritis, pulmonary	19	5	55 (3)	Slight temperature (1, 3)–4 to 5 hrs.; moderate pulse (1, 2)–4 to 5 hrs.; moderate arthritic (1, 2, 3)–24 hrs. râles increased (1)–24 hrs.	Slight antiarthritic	Disease apparently on the upgrade when sodium salicylate was given 2 days later.
22†	B. S.	19	Arthritis	23	3	23 (1)	Moderate temperature, 8 hrs.; rash 24 hrs.; local, 8 hrs.	None at once; after 2 days fever and new murmurs; after a further 4 days pericarditis with effusion.	
23‡	A. S.	30	Arthritis	15	2	16 (2)	Marked dyspnea and cyanosis (2)–5 hrs.; slight temperature and pulse (2)–8 hrs.; marked arthritic (2)–24 hrs.	Slight antipyretic only	Because of poor condition neocinchophen given after 2 days; prompt relief.
24	R. McM.	18	Arthritis	70	8	6 (2)	None	Marked antipyretic; marked antiarthritic	Incomplete recovery; neocinchophen started after fifth day; relapse after 17 days.
25	N. S. (C. R.)	45	Arthritis	27	11	10 (4)	Marked arthritic (1)–24 hrs.	Marked antiarthritic, marked antipyretic	Three days later mild relapse of 6 days' duration; thereafter permanent relief.
26§	P. McD.	13	Carditis, arthritis, pulmonary	3	2	10 (3)	Vomiting (1) several hours	Moderate antipyretic, moderate antiarthritic after first dose only; cardiac and pulmonary condition worse	After 2 days given neocinchophen with prompt antipyretic and antiarthritic effect; other conditions improved more slowly but steadily.

(A) Figures in parentheses indicate days over which total dosage given was distributed.
(B) Figures in parentheses indicate dose after which reaction occurred. Periods of time following dashes indicate interval elapsing before reaction was noted.
* Observation period of only forty-eight hours robs case of value. Not included in Table IV.
† Attempt to desensitize a sensitive patient, with unpleasant sequellæ. Not included in Tables IV, V and VI.
‡ Desensitization unsuccessful; very severe serum shock. Observation period forty-eight hours only, on account of poor condition of patient. Not included in Tables IV, V and VI.
§ Received *unconcentrated* serum. Only forty-eight hours' observation period because rapidly becoming worse.
C. R.—For case report see end of paper.

TABLE IV.—SUMMARY OF THERAPEUTIC RESULTS.*

	No. of patients.	S.C.A. serum.		V110A serum.		Scarlatinal antitoxin.		Totals.	
		Success.**	Failure.	Success.	Failure.	Success.	Failure.	Success.	Failure.
Chorea . . .	1	0	1	..	..	..	..	0	1
Arthritis . . .	12	2	3	0	5	1	1	3	9
Pericarditis . .	3	2†	0	1†	0	..	..	3†	0
Carditis . . .	4	0	2	0	1	0	1	0	4
Totals . . .	20	4††	6	1‡	6	1	2	6§	14

* Does not include Cases 1, 5, 12, 21, 22 or 23.
** The term "success" must be accepted with the qualifications expressed in the text.
† These patients received neocinchophen in addition.
†† Two of these patients received neocinchophen in addition.
‡ This patient received neocinchophen in addition.
§ Three of these patients received neocinchophen in addition.

who states that they attack particularly the smaller joints; in our experience, however, the larger ones have been affected about as frequently as the others. Usually there has been subsidence within twenty-four hours, though in Cases 14 and 18 the condition became progressively worse. In Cases 5 and 11 severe toxemia with delirium followed the use of S.C.A. serum. Less common manifestations have included the appearance of a new murmur, numerous ectopic beats, an increase in pulmonary moisture (râles), and chill, vomiting and other phenomena of protein shock. Dosage of serum, whether large or small, has seemed immaterial; in fact, one of the most alarming reactions occurred three hours after an initial injection of 15 cc. of S.C.A. bovine (Case 11), while in another case delirium of three days' duration set in following the use of 3 cc. of S.C.A. concentrated equine (Case 5). In the latter instance a full course of 10 cc. was given over a period of three days, and large doses of neocinchophen were administered; in addition to the delirium, severe febrile and pulse reactions occurred after each injection of serum, and numerous ectopic beats were observed. A dry pericardial rub of forty-eight hours' duration was noted in Case 10, though it did not appear until three days after the last dose, and consequently cannot fairly be attributed to the serum. Tables V and VI summarize these by-effects. Reactions occurring in "serum desensitized" patients have not been included, as the effect of the factor of serum allergy could not be controlled. As warning against serum treatment of such sensitive individuals may be cited, however, a severe asthmatic attack with deep cyanosis in one patient (Case 23), while in another instance severe carditis, with pericarditis and effusion, developed immediately (Case 22).

TABLE V.—REACTIONS: TABULATED ACCORDING TO SERA.*

	S.C.A. serum.	V110A serum.	Scarlatinal antitoxin.	Totals.
Total doses	31	16	11	58
Temperature	17	5	2	24
Pulse	17	4	2	23
Respiration	5	0	2	7
Cyanosis	1	2	0	3
Delirium	2	0	0	2
Arthritis	5	6	4	15
Shock and chill	1	0	0	1
Ectopic beats	2	0	0	2
Restlessness	0	1	0	1
Dyspnea	0	1	1	2
Vomiting	0	0	1	1
Pulmonary signs	2	0	1	3
Gallop accentuated	1	0	0	1
New murmur	1	0	0	1

* Does not include Cases Nos. 12, 22 or 23.

TABLE VI.—REACTIONS: LISTED ACCORDING TO PRINCIPAL CONDITION.*

	Chorea.	Arthritis.	Pericarditis.	Carditis.	Totals.
Number of patients	1	15	3	4	23
Temperature	1	8	2	2	13
Pulse	1	8	2	1	12
Respiration	0	3	1	0	4
Cyanosis	0	1	1	1	3
Delirium and toxemia	0	1	1	0	2
Arthritis	0	8	1	0	9
Shock and chill	0	0	0	1	1
Ectopic beats	0	1	0	0	1
Restlessness	0	0	0	1	1
Dyspnea	0	1	0	0	1
Vomiting	0	0	0	1	1
Pulmonary signs	0	3	0	0	3
Gallop accentuated	1	1	0	0	1
New murmur	0	1	0	0	1
Patients without reaction—under drug	...	...	1	...	1
Patients without reaction—not under drug	...	2	...	1	3

* Does not include Cases Nos. 12, 22 or 23.

The occurrence of reactions seems to bear no relationship to subsequent improvement or to its permanency.

The danger of such reactions may perhaps be decreased by the simultaneous use of salicylates, which, however, as pointed out above, scientific precision usually forbade during this study. In the few instances cited, in which the condition of the patients seemed to prohibit delay, these drugs have rarely proven efficacious in warding off the reactions, and on one occasion truly alarming symptoms developed (Case 5).

Discussion. Generalizations based on a comparison of the three sera used in this study are hardly justifiable in so small a series of cases. The three different sera were made in as many different laboratories by different methods of immunization, and it is not improbable that had 3 horses or cows been immunized with the same strain of streptococcus by different methods similarly varying results would have been obtained. Hence it is probably better to disregard the effects from any particular serum and discuss them all together. It is, however, noteworthy that comparable symptoms, both favorable and unfavorable, were observed following all three types of serum; and it is not without interest that similar effects were observed over twenty-five years ago by Menzer,[5] Schmidt[6] and Sinnhuber,[7] when a polyvalent antistreptococcus serum prepared by the former was employed. All of these observations lead to the conclusion that any beneficial therapeutic effect observed must be dependent upon some other factor than a specific antitoxin against a hypothetical toxin elaborated by one strain of streptococcus.

Indeed, Menzer,[8] although for years an active proponent of a specific antitoxic action of serum, later attributed the beneficial effect to nonspecific protein therapy ("Reiztherapie"), and hence gave up the use of serum in favor of streptococcus vaccines. His abandonment of serum would appear one of the strongest arguments against its use. But the enthusiastic reports of Baruffaldi,[3] and the observations of Toogood[9] and Barach[10] with antiscarlatinal serum, together with Small's claims, made necessary a further study, with the results as above recorded.

From a theoretic viewpoint it may be asked: were any effects, either beneficial or otherwise, constantly attendant upon the application of these sera, which might be ascribed to their antistreptococcus qualities rather than to their actions as foreign proteins? In the absence of a control group treated simply with normal horse or cow serum a satisfactory answer to this question cannot be given.

Small[11] bases part of his hypothesis of the pathogenesis of rheumatic fever upon focal reactions in the small joints, together with general reactions following serum treatment. He attributed these reactions, which he designates as exudative, to a union of streptococcus antiprotein, contained in all antistreptococcus serum, with streptococcus protein, which he thinks is present in the tissues. Similar focal reactions have been reported following tuberculin treatment[12] and other forms of nonspecific protein therapy; hence this hypothesis demands further testing.

From another theoretic viewpoint one would not expect marked specific beneficial action to follow antistreptococcus serum therapy in rheumatic fever, for it is not of the general type of disease which responds favorably to serum. Usually rheumatic fever is not an acute disease like diphtheria, tetanus, or scarlet fever, but a sub-

acute or chronic infection resembling tuberculosis or syphilis in many of its features.[13, 14]

If a hypothetic toxin or some peculiar bacterial fraction or autolysate is responsible for the various manifestations of the disease, these substances are elaborated in varying amounts and intensity over long periods; hence it is improbable that a serum effect, which at best can be of only short duration, would be ultimately successful. Indeed, Small early recognized this possibility and recommended, in addition, a form of active immunization by repeated subcutaneous injections of an extract of Streptococcus Cardioarthritidis. He has reported better results with the use of this combined method than with the serum alone.

But in spite of these theoretic objections, if consistent improvement followed the application of antistreptococcus serum, one would be compelled to modify his theory, and utilize the serum. Our observations, together with those of Hill[15] and Wilson,[16] however, lead to the conclusion that antistreptococcus serum has no permanent antirheumatic influence, and that acute antipyretic, antiarthritic and antitoxic effects can be more certainly obtained from salicylates or neocinchophen. Whether the favorable effects which followed a combination of these drugs with serum in a few cases of pericarditis were anything more than fortuitous is open to discussion.

Of this one can be certain: that antistreptococcus serum in no way replaced the long-established therapy of rheumatic fever, nor does it apparently add enough to warrant its universal adoption. In our experience the unpleasant reactions sometimes attendant upon its application have not been outbalanced by a reciprocal certainty of therapeutic benefit.

Case Reports. Case 2.—G. H., male aged seven and a half years, admitted March 5, 1928, to the service of Dr. Rivers because of chicken pox developing during the course of rheumatic carditis present at least since November, 1927. March 9, following the subsidence of the varicella, a further rheumatic cycle appeared. By March 14 there were present: temperature 104°, pulse 130, respirations 50, gallop rhythm, mitral and aortic regurgitation, positive Broadbent sign, severe precordial pain and hyperesthesia, hepatic enlargement with severe right upper quadrant pain. On this day S.C.A. concentrated equine serum was given intramuscularly in 3 doses of 10, 8 and 10 cc. respectively, between 12 noon and 9 P.M. No immediate reaction occurred. March 15 no evidence of improvement; similar serum was given, 15 cc. at 10 A.M., and 10 cc. at 6 P.M. During this day the temperature declined to 101.2° and the respiration to 40; no change in pulse rate. During the next three days no improvement; but dullness, bronchial breathing and bronchophony appeared at the angle of the left scapula, and there was cough with mucoid sputum. Neocinchophen therapy was instituted, and resulted in temporary improvement in the cardiac and pulmonary conditions.

Case 4.—S. E., male, aged six years, admitted February 15, 1929, on the third day of his second attack of rheumatic fever; temperature, 102.4°;

pulse, 130; respirations, 24; moderately severe polyarthritis, tonsillar infection, enlargement of heart to left, mitral systolic murmur heard throughout left axilla and left back, accentuated and split P_2, white blood cells 22,000. Under expectant therapy, temperature and pulse remained elevated; February 18, spreading of arthritis and a questionable gallop; 2.5 cc. of S.C.A. concentrated equine serum was given intramuscularly at 2 P.M. At this time temperature was 104.4°, pulse 130, and these levels were maintained throughout the day. February 19 A.M. the arthritis was much more severe; no new joints involved; there was a loud gallop; 2.5 cc. of the same serum was given at 11 A.M. Five hours later the temperature had risen from 103.4° to 104.4° and the pulse from 106 to 128. These levels were maintained throughout the day. The respirations rose to 60. February 20 A.M. the temperature was 102.4°, pulse 110, respirations 36, but during the day rose to 104°, 130 and 62, respectively. Arthritis considerably improved. February 21, fever much the same, though the pulse failed to pass 110° or the respirations 42; the gallop persisted; the patient was free from arthritis, but after a further two days this reappeared and the following morning (February 24) was so severe that neocinchophen administration was begun. At no time during this interval did the temperature fall below 102°, and the pulse constantly ranged from 104 to 120 with the gallop unchanged. At the time of the arthritic relapse the pulse rate increased rapidly, the area of cardiac dullness increased, the murmur became harsh and grating, and the cardiac action became quite tumultuous. The respiratory rate rose to 70, with grunting expiration, and fine râles were heard in the left chest posteriorly. There were no signs of consolidation either by direct examination or by Roentgen ray. The carditis and pneumonitis were at their height February 28, nine days after the completion of the serum course. Four days later a small crop of subcutaneous nodules appeared. The carditis ran a moderately severe course with subsequent marked improvement.

CASE 7.—R. M., male, aged eighteen years, admitted January 2, 1929, on the thirteenth day of his first attack of rheumatic fever; temperature, 105°; pulse, 120; respirations, 36; cyanosis, severe toxemia, mild polyarthritis, small adherent tonsils, precordial hyperalgesia, cardiac enlargement, heart sounds muffled at the apex and over the precordium, loud pericardial friction rub, dullness in lower left axilla, also over the left lower lobe posteriorly merging into flatness at the base, with decreased tactile fremitus, bronchovesicular breathing and numerous moist and fine râles, merging into suppression at the left base, Grocco triangle to the right; roentgenograms indicative of pericardial and pleural effusions. Because of the critical condition neocinchophen was administered; this resulted in a moderate but very fleeting improvement; by January 11 the condition was very serious, and because of intolerance it had become necessary to reduce greatly the dosage of drug. At 2.45 P.M. of this day 5 cc. of S.C.A. concentrated equine serum was given intramuscularly. No reaction occurred. At 2 P.M. temperature was 102.8°, pulse 120; these levels were maintained until 8 P.M., after which a steady decline ensued. January 12 noon, temperature was 99.8°, pulse 104. No subjective or objective improvement was apparent. At 10.45 A.M. 5 cc. of serum was given. By 4 P.M. temperature had reached 103.4°; at 8 P.M. the pulse was 128. Shortly thereafter a decline in both occurred similar to that of the day before. January 13, distinct exacerbation of the polyarthritis; otherwise the general condition was the same, except that the steady loss of weight was checked. Thereafter steady improvement occurred, which by January 18 seemed complete, except for persisting leukocytosis and a small pleural effusion. The latter disappeared following a sharp febrile episode between January 28

and February 1. Drug withdrawal a few days later was followed by uneventful recovery.

CASE 9.—C. K., male, aged thirty years, admitted May 9, 1929, on the fortieth day of the first attack of rheumatic fever; temperature 104°, toxemia, moderately severe polyarthritis, tonsillar infection, short systolic murmur along the left sternal border, palpable spleen. During five days control period fever continued, arthritis spread rapidly, the heart sounds became progressively softer and more distant, and there was steady loss of weight. On May 14, fever slightly lower but arthritis again spreading; 15 cc. of S.C.A. unconcentrated bovine serum was given intramuscularly at 2 P.M. No detectable reaction; the maximum temperature, 102.4° at 6 P.M., was only 0.6° higher than at 2 P.M., May 15, temperature had dropped to 100.2°, the arthritis was much improved and the heart sounds were clearer and louder. At noon 15 cc. of serum was given. At 8 P.M. a sharp rise in temperature to 101.8° occurred, thereafter an equally sharp decline. May 16, the arthritis had largely disappeared, heart sounds quiet and strong, murmur faint, temperature 100.2°. At 2.10 P.M. 20 cc. of serum was given. At 8 P.M. the temperature rose sharply to 101°, then quickly fell. May 17, arthritis in the right arm worse, and by evening the temperature was 101°. On May 19 the temperature once more began to rise and arthritis reappeared; by May 24 the patient was helpless, toxic, rapidly losing weight, with fever above 103°. Neocinchophen promptly controlled the fever and arthritis, and on its discontinuance on June 3 only a moderate shoulder stiffness persisted.

CASE 10.—F. P., male, aged thirty-three years, admitted December 5, 1928, on the fourteenth day of the first attack of rheumatic fever; temperature 103.4°, pulse 104, severe and widespread polyarthritis, ragged tonsils, reddened anterior pillars, palpable tonsillar nodes, soft systolic murmur at apex; leukocytes 27,000. During forty-eight hours of expectant treatment he became steadily worse, temperature hovering at 104° and pulse at 120; *P–R* interval 0.21. December 7, precordial tenderness and gallop rhythm. At 2 P.M. he was given intramuscularly 20 cc. of S.C.A. unconcentrated bovine serum without demonstrable reaction. A steady decline in fever occurred reaching 101.6° at 10 A.M. the following day. Pulse rate and arthritis unaffected, precordial tenderness still present, gallop rhythm less definite; *P–R* interval 0.20. December 8 at 12.15 P.M. he was given 20 cc. of the same serum without demonstrable effect. December 9 fever ranged between 101.4° and 102.4°, pulse 105 to 115, arthritis slightly improved, gallop doubtful, patient less toxic. December 10, however, definite improvement appeared, and by December 16 the temperature was normal, only arthritic symptoms were tender spots about the larger joints; *P–R* interval 0.18, white blood cells 10,640. Precordial tenderness and gallop had disappeared. The periarticular tenderness persisted until after tonsillectomy; otherwise the patient's course was satisfactory. On December 11 and 12 there was a recurrence of precordial tenderness and a dry-friction rub was heard at the left sternal border at the level of the second and third interspaces.

CASE 11.—M. F., male, aged twenty-two years, admitted June 3, 1929, during the twelfth week of the first attack of rheumatic fever; temperature 100.2°, pulse 120, mild polyarthritis, chronic tonsillar infection, systolic precordial heave, systolic impulse and thrill in second left interspace, cardiac enlargement, precordial pain and tenderness, widely transmitted apical systolic murmur, short mid-diastolic puff medial to apex, systolic murmur at base heard in neck vessels. P_2 accentuated and split, systolic and diastolic crunching sounds at level of second interspace, scattered sub-

cutaneous nodules. White blood cells 9,800. During following week he became steadily worse. June 10, pulse 152, widespread erythema multiforme, mushy and muffled first sound, pericardial friction rub, increase in the size of the heart, bronchovesicular breathing and bronchophony at the angle of the left scapula, white blood cell 18,800; increased weight associated with fluid retention. Because of severity of symptoms neocinchophen was started in full doses without inducing antipyresis or amelioration of symptoms in forty-eight hours. June 12, 15 cc. of S.C.A. bovine unconcentrated serum intramuscularly at 11.30 A.M. At 8 A.M. of this day the temperature had been 101.4°, pulse 136; at noon, temperature 102°, pulse 148; at 2 P.M., temperature 103°, pulse 152. By this time the patient was delirious, restless and required restraining; head retracted and head and eyes turned constantly to the right, violent muscular tremors, heart sounds soft and distant, pulse of poor quality, cyanosis of the extremities. No signs of congestive failure. During the day 0.7 gm. digitan was given, and the dosage of neocinchophen was reduced. By evening temperature and pulse were falling sharply and delirium had vanished. June 13 condition improved, diminution in cardiac size, no precordial pain and little tenderness, no signs of compression of the left lower lobe, sticky râles at both bases; 7.5 cc. of serum was given at 10.30 A.M., and at 3.30 P.M. At 10. A.M. temperature was 100.5°, pulse 132; maximum temperature at 2 P.M., 101.8; pulse 136; no untoward reaction. During the night there was a sharp drop in temperature and pulse, which on the following day failed to pass 100.8° and 110 respectively. June 14, 10 cc. of serum was given at 11.20 A.M. and at 3.30 P.M. without demonstrable reaction. Steady and rapid improvement continued. Drug withdrawal on June 16 was uneventful, and the further course was entirely satisfactory.

CASE 17.—A. P., female, aged eight years, admitted January 10, 1929, on the seventh day of her second attack of rheumatic fever; temperature, 105°; pulse, 140; respirations, 44; marked orthopnea, acute polyarthritis, scarred remnants of tonsillar tissue, anterior pillars injected, tonsillar nodes enlarged and tender, diffuse precordial pulsations, cardiac enlargement, loud pericardial friction rub with synchronous thrill, gallop rhythm; over the left lower lobe dullness with bronchial breathing and bronchophony merging into suppression at the base, diminished breath sounds at the right base, white blood cells 33,600; roentgenogram suggests pericardial effusion. Under neocinchophen therapy steady improvement occurred for a week, with disappearance of arthritis, lowering of temperature, pulse rate and leukocyte count, and retrogression of pulmonary and precordial signs. Complete recovery was not achieved, however, and on January 21 an obvious relapse was under way in spite of drug administration. On this day 10 cc. of V110A unconcentrated bovine serum was given intramuscularly at 3 P.M. without immediate reaction. The temperature peak for the day was 102.8° at 4 P.M. followed by a steady decline; pulse little affected. January 22, patient appeared rather better; 10 cc. of the same serum was given at 2.40 P.M. No demonstrable reaction occurred. The temperature peak for this day was 100.5°; pulse ranged between 120 and 140. Except for a rise in temperature to 102.8° on the evening of the twenty-third the course during the ensuing two weeks was one of steady improvement, with disappearance of all signs of pericarditis and pulmonary involvement, decline in tachycardia, decreasing leukocytosis, diminution in cardiac area, and normal or only very slightly elevated temperature. Drug withdrawal at the end of this period was uneventful. The patient entered then upon a prolonged subfebrile course, free from acute episodes.

CASE 19.—W. F., male, aged forty-one years, admitted February 20, 1929, on the twenty-fourth day of the first attack of rheumatic fever; temperature 100.6°, pulse 90, severe polyarthritis, congested fauces and pharynx, short systolic murmur at the base to left and right of the sternum, soft, diastolic murmur in 2d, 3d and 4th left interspaces; blood pressure 115 systolic, 40 diastolic; white blood cells 17,400. During the next forty-eight hours the temperature rose to 103.8° and there was spreading arthritis. February 22 at 11.30 A.M. he was given intramuscularly 20 cc. of V110A unconcentrated bovine serum without demonstrable effect on fever or pulse. February 23 at 8 A.M. temperature was 101.8°, pulse 88; the arthritis had ceased to spread but was more severe in the right hand; 20 cc. of serum at 11.30 A.M. During the day the temperature rose to 103.8°, the pulse to 100. February 24, the temperature was 100.8°, pulse 90. Most of the previously involved joints were improved; on the other hand, a few were worse and there was reinvolvement of joints which had been free for some time. During the day the temperature rose rapidly to 103.6°, to fall sharply during the night. February 25, there was considerable improvement, except for the newly involved joints of the day before, in which the process was at its height; February 26, these in turn had begun to yield and general improvement was quite marked. The temperature never became normal, however, and during the period February 27 to March 2 the febrile course was renewed; widespread and severe polyarthritis developed, and rapid loss of weight occurred. Neocinchophen therapy was instituted upon the latter day and a very prompt and gratifying improvement ensued. Except for a mild relapse attendant upon premature withdrawal of drug, the remainder of the patient's course was uneventful.

CASE 25.—N. S., male, aged forty-three years, admitted April 8, 1929, on the sixteenth day of his fifth attack of rheumatic fever; temperature 102.8°, pulse 92, moderately severe polyarthritis, chronic tonsillar infection, systolic murmur at apex poorly transmitted outward, systolic murmur in second left interspace, radial arteries slightly thickened, blood pressure 152 systolic, 85 diastolic. During a control period of ten days the disease was irregularly continuous, temperature 100.6° to 103.6°, pulse 90 to 100, arthritis never absent and at times very severe, steady loss of weight and strength. April 19, 3 cc. of concentrated scarlatinal antitoxin was given intramuscularly at 4.15 P.M. without immediate reaction. At 4 P.M. temperature was 101.6°; at 6 P.M., 102°; it declined steadily during the night. Similar declines had occurred nightly during the control period, so that the A.M. temperature of 100° was no lower than usual. The pulse hovered around 110°, about 6 points higher than usual. The morning of April 20 there was a severe exacerbation of the arthritis, with spreading to the hips and knees. At 10.45 A.M. 3 cc. of antitoxin was given. There was no reaction, and during the day the temperature failed to surpass 101°. April 21, arthritis considerably improved, and fever did not exceed 100.6°. The weight loss was checked. April 22, the relief was more pronounced; 4 cc. of the antitoxin was given at 2.30 P.M. without reaction; temperature not above 100°; pulse range 110 to 120. Improvement continued for three days; there was then a five-day cycle of serum sickness with small-joint arthritis and urticaria. Following the spontaneous subsidence of this episode the further course was entirely satisfactory.

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BLOOD TRANSFUSION IN THE ACUTE INFECTIOUS DISEASES.

An Analysis of 100 Cases.

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(From the Willard Parker Hospital.)

The purpose of this article is to evaluate the transfusion of blood as a therapeutic agent in the treatment of the acute infectious diseases, their complications and sequelæ. One hundred cases in which transfusions were performed at the Willard Parker Hospital have been studied in an effort to attain more concrete knowledge as to the type of infectious diseases which is benefited by transfusion. The literature affords little information on this subject at present.

Both the direct (chiefly Lindeman) and the indirect methods of transfusion were employed. Without going into the controversy as to the relative efficacy of the two measures, it may be

stated that from our observation at the Willard Parker Hospital the direct method is the method of choice, provided members of the staff can be sufficiently trained to carry out the technique. The indirect method (citrate) is much employed and is in wide use at many excellent institutions, and, although admittedly attended more frequently by reactions of greater severity (in this series in the ratio of 5 to 1), it is simpler and should be the method of choice in a contagious disease hospital, if, due to the constantly changing nature of the staff, adequate instruction and experience in the direct method is not practical, or if the more complicated method interferes with carrying out the hospital aseptic technique, the purpose of which is the prevention of crossed infections.

The 100 cases studied cover a period of three and a half years, from January 1, 1926, when transfusions began to be regularly done, to May 1, 1929. Of the 100 cases analyzed, 35 died and 3 showed no improvement. During their stay in the hospital, the majority of these patients were, at one time or another, critically ill. In many instances, of course, transfusion was instituted to combat the complications rather than the primary disease. In the following tables, blood counts are not included because of the inadequacy of the records in this respect.

Diphtheria. Of 27 cases of diphtheria transfused, 15 died, a mortality of 55.5 per cent. (Cases No. 259 and No. 1948 had positive throat cultures, but not clinical diphtheria, and hence are not included.)

There were 9 cases of laryngeal diphtheria of which 2 (Cases No. 3140 and No. 2087), both uncomplicated, were transfused twenty-eight and twenty-seven days respectively after admission. Here the primary disease was already cured, the transfusion being employed as a tonic measure, and therefore these 2 cases are not included in computing the mortality for laryngeal diphtheria. Of the 7 remaining cases of laryngeal diphtheria, 4 died, a mortality of 57.1 per cent. Of these, 2 cases, Case 2949 complicated by empyema, Case 3118 complicated by bronchopneumonia, were reported as doing well until transfused, and died within twenty-four hours after the transfusion. Case 158, very toxic, died four days after transfusion, and Case 3006, complicated by bronchopneumonia, twelve days after transfusion.

Of the 3 cases improved or cured, in one, Case 2459, there was immediate improvement following transfusion and subsequent cure. No. 4559 complicated by bronchopneumonia, improved; and in Case 2371 the transfusion on two occasions was not completed because of very severe immediate reactions.

In short, in only 1 case of laryngeal diphtheria, Case 2459, can the transfusion be said to have been in any sense a life-saving measure. On the other hand, in 2 cases, death was probably hastened or precipitated by transfusion, while in the remaining cases no conclusion can fairly be drawn.

TABLE I.—DIPHTHERIA.

Hosp. No.	Date of admission.	Sex.	Age.	Complications.	Transfusion.			Reaction.	Results.	Remarks.
					Date.	Method.	Amount.			
1926.										
2459	10/13	M.	1 yr.	Laryngeal	10/16	I.	150	None	Cured	Respirations up to 70 before transfusion.
2820	12/13	M.	6 yrs.	Tonsillar; myocarditis	12/15	I.	210	None	Died	Myocarditis developed 2 days after transfusion; died 3 days after transfusion.
1927.										
170	1/20	F.	4½ yrs.	Tonsillar and pharyngeal	1/24	I.	200	None	Died	Died in 24 hours.
273	1/30	M.	19 mos.	Bilateral otitis media	2/4	I.	150	None	Cured.	
2087	6/17	F.	17 mos.	Laryngeal	7/14	I.	200	None	Cured	Tonic.
2371	7/17	M.	1 yr.	Tonsillar and laryngeal; toxic	7/19	I.	125	Severe	Not improved	Very toxic.
					8/4	I.	75	Severe		Both stopped because of severe reactions.
2415	7/27	M.	1 yr.	Tonsillar and nasal	8/3	D.	200	None	Cured.	
2863	10/25	M.	4½ yrs.	Tonsillar; myocarditis	10/28	I.	180	Slight	Died.	
					10/29	I.	160	None.		
3006	11/15	F.	1 yr.	Laryngeal; bronchial pneumonia	11/18	I.	150	None	Died.	
3118	12/1	F.	2½ yrs.	Laryngeal; bronchial pneumonia	12/9	I.	....	None	Died	Doing well until transfusion; died in 24 hours.
3164	12/7	F.	12 yrs.	Toxic; heart block	12/9	I.	250	None	Died	Six days after transfusion developed heart block.
1928.										
55	1/7	F.	5½ yrs.	Nasal and tonsillar diphtheria	1/9	I.	200	None	Cured.	
541	2/11	M.	2 yrs.	Tonsillar diphtheria	2/29	D.	200	None	Cured.	
1031	3/9	F.	2 yrs.	Tonsillar; S.F.; erysipelas; bronchial pneumonia	3/30	D.				
					4/26	D.	240	None	Cured	Transfusion succeeded where S.F. antibacterial vaccine and erysipelas antitoxin failed.

2949	5/25	M.	2½ yrs.	Laryngeal diphtheria; empyema	6/21	D.	120	None	Died	Marked anemia.
3140	12/4	M.	3½ yrs.	Laryngeal and pharyngeal diphtheria	1/24	D.	100	None	Improved.	
4203	8/23	M.	7 mos.	Pharyngeal diphtheria; myocarditis; acute intestinal intoxication	8/24	?	200	None	Died 9/10	Probably died of intestinal intoxication.
4559	10/27	M.	2 yrs.	Streptococcic sore throat	10/17	D.	260	None	Cured.	
1929.										
158	1/10	M.	27 yrs.	Laryngeal diphtheria; bronchial pneumonia	1/12 1/19	D. D.	300 320	None None	Died in 4 days	Tracheotomy.
259	1/15	F.	3 yrs.	Diphtheria by culture; rickets; pulmonary tuberculosis	1/21	D.	175	None	Cured	Very anemic.
1007	3/6	F.	2 yrs.	Nasal; cervical adenitis; streptococcus septicemia	3/11	D.	260	None	Died 3/11	
1321	3/22	F.	25 yrs.	Toxic diphtheria, pharyngeal; myocarditis	3/23	D.	500	None	Died 3/24	Myocarditis before transfusion.
1452	3/28	F.	8 yrs.	Nasal and tonsillar diphtheria, toxic; multiple neuritis; rheumatic heart disease; myocarditis	3/30	D.	400	None	Not improved	Taken home against advice; persistent nasal bleeding; myocarditis developed.
1510	3/31	F.	4½ yrs.	Tonsillar and laryngeal; acute streptococcic sore throat; bronchial pneumonia	5/9	D.	200	None	Died	Died within 24 hours of transfusion; died of streptococcic throat.
1543	4/1	F.	2½ yrs.	Nasal; myocarditis	4/2	D.	200	None	Died 4/2	Persistent nasal bleeding.
1642	4/6	M.	2 yrs.	Tonsillar diphtheria; bronchial pneumonia; right otitis media	4/19	D.	200	None	Cured	Transfusion brought temperature to normal.
1669	4/8	F.	20 yrs.	Tonsillar and palatal diphtheria, toxic	4/12	D.	200	None	Cured	
1948	4/24	M.	10 mos.	Diphtheria by culture; otitis media; mastoiditis	5/11	D.	220	None	Cured	Reinfection of old mastoid, not operated.
5167	12/29	M.	4 yrs.	Toxic diphtheria; mastoiditis; myocarditis	1/31	D.	200	None	Died 2/2	Throat filled with mucus at time of transfusion; very toxic.

NOTE.—Improvement means that the case left the hospital either at the patient's own risk, or was transferred to a general hospital before a cure was effected. Practically without exception these cases were out of danger when released or transferred.

TABLE II.—SCARLET FEVER.

Hosp. No.	Date of admission.	Sex.	Age.	Complications.	Transfusion.			Reaction.	Results.	Remarks.
					Date.	Method.	Amount.			
1926. 2398	9/28	F.	2½ yrs.	Tuberculous glands with sinus	10/18	I.	250	None	Improved	Dehydration, anemia.
1927. 91	1/13	F.	2½ yrs.	Empyema	1/24	I.	165	None	Much improved.	
353	2/9	F.	6 yrs.	Cervical adenitis; mastoidectomy	2/11	I.	200	None	Died	Died within 24 hours.
1140	4/4	F.	2 yrs.	Otitis media, empyema	4/7	I.	150	None	Cured.	
1184	4/7	F.	3 yrs.	Foreign body in bronchus; otitis media; serum rash	4/23	I.	150	Moderate	Cured.	
1388	4/20	F.	2½ yrs.	Diphtheria	4/26	I.	125	Slight	Much improved.	
2527	8/18	F.	12 mos.	Otitis media; nephritis	8/28	I.	250	Slight	Improved	Home on release.
1928. 620	2/16	F.	2 yrs.	Bronchial pneumonia; empyema	3/14 3/19	D. D.	140 150	None None.	Cured.	
1663	3/8	F.	9 yrs.	Bronchial pneumonia; empyema	3/25	D.	....	None	Cured.	
1811	4/9	F.	25 yrs.	Dementia precox; bronchial pneumonia	4/15	D.	500	None	Died 4/17	Very toxic; no improvement.
2463	5/5	M.	2½ yrs.	Mastoidectomy	5/28	...	250	....	Cured	Moderate anemia.
3071	11/23	F.	3 yrs.	Mastoiditis	11/27 11/29	I. I.	220 160	None None	.... Cured	Moderate anemia, hemoglobin 60 per cent; red blood cells, 2,300,000.

3150	6/1	M.	4 yrs.	Empyema and multiple abscesses; otitis media; nasal diphtheria	6/21 ..	D. D.	250 200	None	Improved	Home on release.
3345	12/30	F.	6	Mastoiditis	1/3	I.	100	Moderate	Cured	1/26/29, hemoglobin 70 per cent; red blood cells, 4,640,000.
3532	4/19	F.	15 mos.	Bronchial pneumonia, catarrhal laryngitis; septicemia	6/29	D.	225	Marked	Died.	
4418	10/7	F.	30	Acute mastoiditis; otitis media	10/18	I.	200	None	Cured	Transfusion stopped because of clot.
4624	11/6	F.	10	Otitis media; cervical adenitis	12/1	D.	300	None	Cured.	
4707	11/14	M.	7	Double mastoiditis	11/15 11/22	D. D.	300 280	None	Cured.	
1929. 1160	3/14	M.	5	Septicemia	3/16 2/27	D. D.	320 180	None	Died 3/16	Acute septic.
1261	3/9	M.	6	Lobar pneumonia	3/20	D.	120	None	Died	Admitted on twenty-third day of illness; developed pneumonia 10 days after transfusion.
1282	3/20	F.	28	Sepsis; bronchial pneumonia; pleurisy; lung abscess	4/22	D.	550	None	Died 4/25	
1530	4/1	M.	3½	Lobar pneumonia; empyema and gangrene of lung	4/20	D.	320	None	Died	Very toxic.
1563	4/2	F.	2	Bronchial pneumonia; bacteremia	4/4	D.	230	None	Died	No improvement.
1891	4/21	F.	15	Toxic scarlet fever	4/24	D.	470	None	Died 4/25	Given too much blood.
5185	12/29	M.	14	Mastoiditis; right sinus thrombosis	2/1	I. I.	476 500	None None.	Cured	

TABLE III.—MEASLES.

Hosp. No.	Date of admission.	Sex.	Age.	Complications.	Transfusion.			Reaction.	Results.	Remarks.
					Date.	Method.	Amount.			
1926.										
1355	4/27	M.	2½ yrs.	Scarlet fever; otitis media; bronchial pneumonia	5/19	D.	150	None	Cured.	
1415	5/3	M.	11 mos.	Bilateral otitis media; bronchial pneumonia	5/26	D.	150	None	Cured	Mastoidectomy 6/22; anemia marked; had pneumonia on admission.
1654	5/27	F.	6 yrs.	Acute appendicitis, operated	6/1	I.	120	None	Improved	Vomited ascaris lumbricoides following operation.
1663	5/28	F.	9 mos.	Bronchial pneumonia; bilateral otitis media	6/4	I.	75	None		
					6/7	I.	50		Died 6/9	
1710	6/1	M.	3 yrs.	Otitis media; bronchial pneumonia; pyelitis	6/24	I.	172	None	Cured	Anemia.
2496	9/20	F.	2 yrs.	Pertussis; left conjunctivitis; bronchial pneumonia	10/27	I.	180	None	Improved.	
1927.										
1722	9/13	F.	9 yrs.	Bronchial pneumonia	6/4	I.	100	None	Died.	
1729	5/17	F.	2 yrs.	Bronchial pneumonia; otitis media	6/8	I.	65	None	Much improved	Saved life.
					6/11	I.	110	None		
1765	5/19	M.	6 mos.	Otitis media; bronchial pneumonia; empyema; mastoiditis	6/22	I.	115	Marked	Much improved	Home on release; temperature normal.
1866	5/17	M.	11 mos.	Otitis media; mastoiditis; bronchial pneumonia	5/30	I.	50	None	Cured	No operation.
					7/14	I.	150	Slight		
1928.										
169	1/16	F.	1 yr.	Bronchial pneumonia; otitis media	2/3	I.	85	None	Cured.	
1565	3/20	F.	3 yrs.	Mastoiditis; arthritis, left knee	4/30	D.	200			
					5/6	D.	160	None	Cured	Tonic.
2403	5/2	M.	1½ yrs.	Cervical adenitis	5/16	D.	180	None	Improved	Cured.
3210	6/3	F.	2 yrs.	Bronchial pneumonia; otitis media	7/19	I.	205	None	Improved	Cured.
3632	6/26	M.	11 mos.	Otitis media; bronchial pneumonia	7/31	I.	220	Improved	Improved	Discharged on release.
3647	6/27	M.	16 mos.	Bronchial pneumonia	7/22	D.	220	None	Improved.	
3677	6/29	F.	6 yrs.	Cerebrospinal meningitis	7/7	D.	350	None	Died.	
4031	2/2	M.	7 yrs.	Pneumonia; otitis media	2/15	I.	180	None	Cured.	
2249	6/2	..	...	Uncomplicated	6/29	I.	300	None	Cured	Tonic.

4031	2/2	M.	7 yrs.	Pneumonia; otitis media	2/19	I.	100			
2249	6/2	..	...	Uncomplicated	6/29	I.	300	None	Cured	Tonic.

TABLE IV.—PERTUSSIS.

Hosp. No.	Date of admission.	Sex.	Age.	Complications.	Transfusion.			Reaction.	Results.	Remarks.
					Date.	Method.	Amount.			
1926.										
2227	8/16	M.	4 mos.	Gastroenteritis	9/13	I.	75	None	Cured	Dehydration; anemia.
2520	10/28	M.	2½ yrs.	Bronchopneumonia	19/19	I.	160	....	Cured	Followed by crisis.
1927.										
2652	9/14	M.	18 mos.	Bronchopneumonia	9/23	...	100	Severe	....	Transfusion stopped because of collapse.
					9/28	I.	150	Slight	Died	
2662	9/15	M.	14 mos.	Bronchial pneumonia; rickets; convulsions	9/17	I.	150	Slight	Improved	No convulsion after transfusion; temperature 106.6° at one time, plus convulsions.
2808	10/17	M.	1 yr.	Gastroenteritis; dehydration	10/20	I.	125	Slight	Cured.	
2841	10/22	F.	3 yrs.	Bronchial pneumonia	10/27	I.	200	None	Cured.	
2880	10/27	F.	14 mos.	Bronchial pneumonia; otitis media	11/6	I.	200	Moderate	Cured.	
2960	11/8	M.	6½ mos.	Stomatitis; acute otitis media; bronchial pneumonia	11/15	I.	180	Moderate	Cured.	
3068	11/23	F.	2½ yrs.	Bronchial pneumonia; malnutrition	12/6	I.	40	None	Cured.	

TABLE V.—MISCELLANEOUS.

Hosp. No.	Date of admission.	Sex.	Age.	Complications.	Transfusion.			Reaction.	Results.	Remarks.
					Date.	Method.	Amount.			
1926.										
2599	11/9	F.	2½	Foreign body, left bronchus	11/10	I.	50	None	Died	Chestnut shell in bronchus.
1927.										
1918	6/1	F.	13 mos.	Streptococcic septicemia; bronchial pneumonia	6/8	I.	80	None	Died.	
2240	7/2	F.	55	Streptococcic septicemia	7/6	I.	500	None		
					7/12	I.	500	Slight	Improved	Erysipelas.
2441	8/2	F.	4	Poliomyelitis (bulbar)	..	I.	150	None	Not improved	Home on release; intraperitoneal used; intravenous failure.
2456	8/5	M.	8	Poliomyelitis and respiratory paralysis	8/13	I.	225	None	Died	
2493	5/6	M.	6	Postmeasles encephalitis	5/7	D.	400	None	Died	In coma when transfused; died 4 hours after second.
					5/9	D.	300	None		
2627	8/15	M.	5	Typhoid fever; bronchial pneumonia	9/13	I.	200	Marked	Cured.	
2658	9/14	M.	14	Typhoid fever	10/7	I.	180	None	Cured	Blood culture, Gram-positive diplococci.
2678	9/19	F.	14 mos.	Retropharyngeal abscess (bilateral); rickets	9 21	I.	150	Slight	Cured.	
2761	10/5	F.	14 mos.	Abscess, right buttock; rickets; malnutrition; naso-pharyngitis	10/8	D.	200	None	Improved	Hematuria.
2967	11/10	F.	20 mos.	Lobar pneumonia; otitis media bilateral; meningismus	11/14	I.	100	Moderate	Cured.	
1928.										
202	1/19	F.	2½	Streptococcic throat; meningitis; bronchial pneumonia	1/25	I.	200	Died.		
400	2/2	M.	10½	Poliomyelitis (bulbar)	2/7	D.	350	None	....	Critically ill; died 2 hours after transfusion.
2669	5/13	F.	35	Acute sinusitis; otitis media; mastoiditis; lateral sinus thrombosis; septicemia and meningitis	6/8	D.	500	None	Died	Moribund when transfused.
					6/15	D.	500	None		
4488	10/17	M.	2	Streptococcic sore throat	10/17	D.	260	Improved	Cured.	
1929.	*Varicella.*									
436	1/24	F.	18 mos.	Cellulitis	2/3	D.	160	None	Improved	Transferred to Bellevue.
519	1/31	F.	18 mos.	Varicella; bronchial pneumonia; cellulitis, chest wall	2/1	D.	200	None	Died	Died 3 days after transfusion.
864	2/24	F.	5 mos.	Varicella; gastroenteritis; otitis media	3/1	D.	100	None	Improved	Transferred to Bellevue.

Of the 27 cases of diphtheria transfused, there were 8 cases designated as toxic. Of these, 4 died, another probably died outside the hospital, 2 were cured, and 1 improved.

From experimental work on cats and rabbits, Harding[1] has concluded that transfusion may be of some value in the toxic stage of diphtheria. However, the results just quoted hardly bear out this theory.

Seven cases in which myocarditis was present or developed, were transfused. Of these, 6 died, and 1 was released against the advice of the hospital in a moribund condition. Three died within twenty-four hours after transfusion. Two cases developed myocarditis after transfusion, three to six days respectively, the remainder having had evidences of myocarditis before transfusion.

In short, transfusion neither was of aid in preventing injury to the myocardium nor successful in saving the lives of those patients in whom myocarditis was present, so it appears that transfusion is absolutely contraindicated in diphtheria complicated by myocarditis, simply throwing an unnecessary burden on the weakened heart muscle, and of no value and probably harmful in laryngeal diphtheria, especially at the height of the disease or when bronchopneumonia is present. Transfusion appears to be of benefit in protracted cases in which malnutrition or anemia develops (Cases 2087 and 3140).

Scarlet Fever. Of 25 cases of scarlet fever that were transfused, 9 died, a mortality of 36 per cent. Of the 9 deaths, 3 cases died of the uncomplicated primary disease. Transfusions had no effect whatever on the course of these acute toxic scarlatinas, 2 dying within twenty-four hours and the third three days after transfusion.

Of the remaining 6 cases which died one was complicated by lobar pneumonia, empyema and gangrene of the lung. There were 3 deaths from bronchopneumonia, but 2 of these cases were complicated by septicemia and bacteremia and the third was a very toxic case which would probably have succumbed anyway. In this connection, Stetson[2] has reported 10 recoveries in 19 transfused cases of Streptococcus hemolyticus bacteremia. Warren and Herrick,[3] on the other hand, report only 10 recoveries in 31 cases which were not transfused.

Of the 16 cases which were improved or cured, there were 2 cases complicated by empyema, 2 cases complicated by bronchopneumonia and empyema, 3 cases of cervical adenitis, 7 cases of mastoiditis, of which one had a sinus thrombosis. There were no deaths from mastoiditis in the transfused cases. Both in preparing patients for mastoidectomy and as an adjuvant in convalescence, transfusion seems to have won a well-merited place. In Case 5185, complicated by sinus thrombosis, which was seen by the writer, there was little doubt but that the transfusion was life-saving.

Feinblatt[4] also has had excellent results with transfusions in cases of sinus thrombosis.

Its use also seems justified in the pre- and postoperative cases of empyemas. Of the 2 cases listed which died, one was moribund when transfused and the other developed gangrene of the lung.

Again, as a general tonic late in convalescence when the patient has become badly malnourished or anemic, or in the more protracted types of complications such as cervical adenitis or nephritis, transfusion appears to be of use. Its value against bronchopneumonia cannot be judged because of the complicated nature of the cases studied in this group.

Measles. Of 19 cases of measles transfused, 3 died, a mortality of 15.8 per cent. Of the 3 deaths, Case 1722, complicated by bronchopneumonia, died twenty-four hours after admission, Case 1663, complicated by bronchopneumonia and otitis media, died two days after the last of two transfusions, and Case 3677 developed cerebrospinal meningitis. Of the 15 cases which improved or recovered, 9 complicated by bronchopneumonia were transfused seven to forty-six days after admission, the average being twenty-five days. Two cases complicated by empyema and 3 by mastoiditis were improved or cured.

Transfusion in measles appears to be of definite value in the cases complicated by bronchopneumonia. The results also justify its use in empyema and mastoiditis.

NOTE.—This mode of treatment should not be confused with the intramuscular injection of convalescent serum or whole blood, which was extensively tried out by Zingher[5] at this institution several years ago.

Pertussis. Of the 9 cases of pertussis transfused, one died, a mortality of 11.1 per cent. The one death, Case 2652, may probably be attributed directly to the transfusion, as the patient went into collapse while being transfused.

The 7 cases which improved or were cured, were transfused on the second to the twenty-fourth day after admission, the average being twelve days. Five of these cases were complicated by bronchopneumonia and 2 by gastroenteritis. In general, it may be said that the bronchopneumonias reacted well to transfusion, there being but one death in 6 such complicated cases, but that it is not unattended by danger is shown by the collapse in the instance of Case 2652.

Miscellaneous. Three cases of the bulbar type of poliomyelitis were transfused, with 100 per cent mortality. Three cases of varicella in infants were transfused, of which one died three days after transfusion, 2 were improved and transferred to Bellevue Hospital. There were 2 cases of typhoid fever, both of which were cured. Ottenberg and Libman,[6] on the other hand, report recovery of only 2 out of 9 patients critically ill with typhoid. Two cases of strepto-

coccus septicemia were transfused with one recovery. One post-measles encephalitis died four hours after transfusion.

Summary. 1. Blood transfusion appears to be contraindicated in diphtheria complicated by myocarditis, and in laryngeal diphtheria particularly when bronchopneumonia is present.

2. It is a valuable adjuvant in the pre- and postoperative care of mastoiditis, sinus thrombosis and empyema, particularly when these conditions are complications of scarlet fever or measles.

3. It is of value in the treatment of bronchopneumonia complicating measles and pertussis.

4. As a general tonic in protracted cases in which anemia and malnutrition develop its use is strongly indicated.

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ON SOME VENOUS MURMURS FOUND IN HEPATIC CIRRHOSIS AND THEIR CONFUSION WITH MURMURS OF CONGENITAL HEART DISEASE.

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TORONTO.

Only some detail of special interest can justify further discussion upon the nature of venous murmurs; well recognized since the time of Laennec and Bouillaud, described as occurring under many and different circumstances, and in so many of the hidden corners of the body, we have come to look upon them as mere matters of passing interest. Placed in certain situations, however, a venous murmur has been known to create some difficulty in diagnosis, as is evidenced by the description of Palmer and White[1] of the sounds which may be produced in the innominate and superior caval veins by the flow from the internal and external jugulars. The fact, stressed in their description, that some of the loud continuous murmurs heard over the upper sternum and down about the second and third right intercostal spaces can be obliterated by pressure upon the external jugular, does not seem to be a matter of general

recognition, and those interested in venous murmurs which may be so placed as to suggest some congenital affection of the heart should consult the excellent résumé given by these writers.

Palmer and White bring the venous murmurs arising from the confluence of the jugulars, the subclavians and the innominates down to the upper heart limits, while Thayer,[2] working from below, so to speak, brings the venous hums of the abdomen, those so often recorded in association with cirrhosis, up to the lower heart borders, including in his discussion the description of one murmur, presumably of venous origin, which could be followed from the xiphoid area to the episternal notch. This particular instance of a venous murmur developing over the heart area in the course of a hepatic cirrhosis, another recorded by Fell[3] subsequent to a wound of the sternum and those of my own would seem on the one hand to bridge the gap as concerns the placing of a venous hum directly over the heart area, and on the other to excuse the somewhat incomprehensible title of this contribution.

As has been indicated, I am not attempting in this short report to discuss the causes of venous murmurs, but wish to describe the conditions which existed in 2 rather remarkable cases which had been considered cases of congenital heart disease, until it was shown that the confusing murmur could be completely removed by the simple process of laying a finger upon the spot over the heart area, under which a hidden vein was coursing.

Murmurs developing in association with the varicosities which we know to exist when cirrhosis of the liver has progressed to a certain degree are not uncommon.[4] They usually belong, however, to the region of the ensiform cartilage or the subdiaphragmatic areas, and have been readily explained when once the existence of cirrhosis with its venous dilatations has been recognized. In some few instances dissection has shown an arrangement of venous channels,[5] which seemed to be such that it could explain the remarkable murmurs heard while circulation was going on; it might be difficult, however, to fix a murmur heard during life upon any arrangement of empty nonfunctioning vessels disclosed by examination after death. In the cases to be detailed a simple procedure seemed to throw much light on the "point of origin" at least of two oddly placed venous murmurs, while the fact, that in both instances the diagnosis of congenital heart disease could be absolutely excluded by the same simple procedure, seems not without some degree of interest.

Beginning with a description of the second case, who is still alive, it will be enough to say that he was presented at a clinic gathering as a case of congenital heart disease, because of the loud roaring continuous murmur heard over the base of the heart and toward the foot of the sternum. The murmur suggested by its qualities, position and disposition the existence of some gross defect

in the cardiac septa, and those interested in the presentation of the case inclined to the idea of a defect in the interventricular septum. Other possibilities connected with the heart were naturally considered, and a striking coincidence was a systolic murmur about and to the left of the abdominal aorta in its lower part. The patient gave a history of alcoholism, his spleen was much enlarged and his liver was easily felt. Further details of the case are that there is no cyanosis and no clubbing of the fingers. The absence of these physical signs, however, by no means rules out the possibility of congenital heart lesion, and there was certainly the tendency to associate the much-enlarged spleen and the large liver with a degree of chronic passive congestion, although there was no sign of edema in the lungs, abdomen or extremities. The murmur as charted seemed best heard just to the left of the midsternum at the level of the fourth interspace. It was loud roaring and with a systolic intensification; it was associated with a distinct thrill, and was transmitted a considerable distance in all directions, but not particularly into the vessels of the neck or to the pulmonary artery district. It could be heard in the back, and seems to conform to the description of murmurs which result from defects in the auricular or ventricular septum. All the questions, however, as to the point of origin of the murmur, and its meaning, seemed to be answered by the fact that the lightest possible pressure at the point indicated in the picture Fig. 1 causes the murmur to disappear at once. This, of course, tells one that it has nothing to do with a heart condition and promotes at once further investigation.

Palpation of the sternum discloses a slitlike fissure just to the left of the midline, and one sees that the point at which a gentle pressure will obliterate the murmur is immediately above this fissure. The probability is that a vein is discharging through this fissure to pour into larger venous channels beneath and is meeting other currents in such manner that a murmur is produced. The history of alcoholism, the large liver, the large spleen suggest at once the existence of hepatic cirrhosis or portal thrombosis, and one surmises that in this case we are dealing with one of the curious anomalies which at times may be met with in the development of a collateral circulation, an anomaly doubly interesting from the fact that its point of discovery is placed high enough to cause confusion with certain murmurs which are held to suggest congenital heart disease.

The suggestion that pressure about this or that area might influence the murmur followed naturally from experience in connection with other venous hums. In the following out of one we found that slight pressure upon the external jugular vein caused the disappearance of a loud roaring murmur heard in the first and second right interspaces, over the right heart border and behind the right

shoulder.[6] In the consideration of another, one which imitated closely in quality and distribution the murmur already described, and which in turn had suggested congenital heart disease, we were able to see the structural conditions, which at least contributed to the auscultatory findings.

In the AMERICAN JOURNAL OF THE MEDICAL SCIENCES (1912, **143**, 72) is described a case which I had the pleasure of dissecting for Dr. J. Norman Henry, of Philadelphia. We had watched the patient for many months, interested in a loud roar at the lower

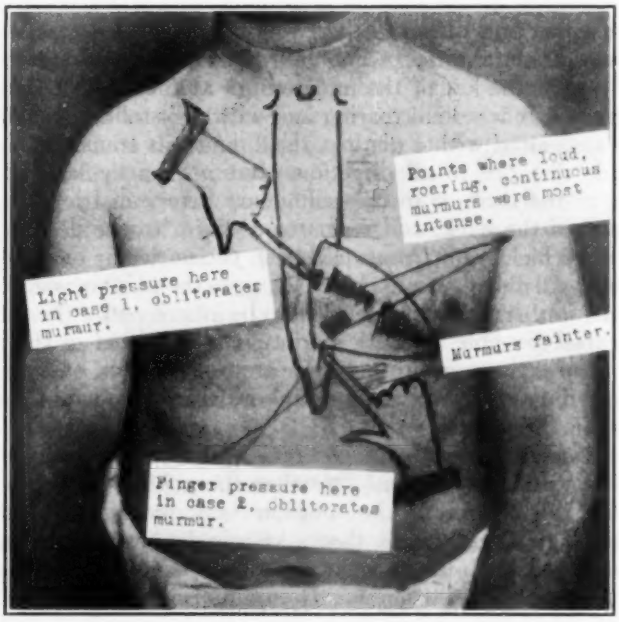
Points where loud, roaring, continuous murmurs were most intense.
Light pressure here in case 1, obliterates murmur.
Murmurs fainter.
Finger pressure here in case 2, obliterates murmur.

FIG. 1.—Diagrammatic sketch, showing the situation of fissures in the sternum and points at which the murmurs were best heard in the two cases reported. These fissures which result from some disturbance of the proper process of ossification in the sternal segments are very common. A developing collateral circulation in the course of cirrhosis would be very likely to find a way through any such deficiency.

sternal area, continuous, heard over the precordium and showing slight intensification both with inspiration and with the heart systole. We had in our turn made the mistake of inclining to the idea that this murmur represented congenital heart disease rather than a hum produced in the veins. The position of the murmur, well above the xiphoid, and its systolic intensification were the points which influenced us most. The diagnosis for many weeks remained "case of defect of interventricular septum." Quite by accident we discovered that slight pressure of the finger at the

point indicated (Case I) Fig. 1, completely obliterated the murmur, although at this time there was little if any sign of venous dilatation or obstruction. As the months went on the picture of cirrhosis of the liver was faithfully reproduced: the liver enlarged, the spleen projected from below the costal margin and veins could be seen coursing upward to the epigastric and sternal areas as well as downward to the groin. Pressure on one particular vein could be shown to regularly obliterate the murmur. As in the case described in the same year by Dr. W. S. Thayer,[2] this murmur disappeared of itself a few hours before death.

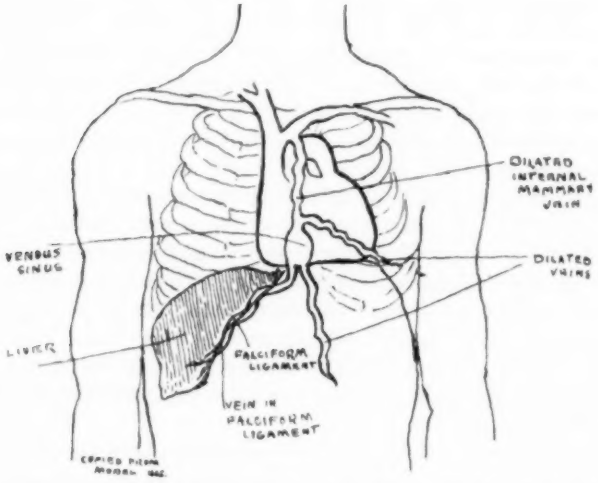

FIG. 2.—Diagrammatic representation of conditions which may be present in some instances of well-developed collateral circulation and of the condition found in Case II. The liver and falciform ligament are indicated as is the vein coming from the ligament through the diaphragm. The venous sinus is roughly represented as lying over the lower part of the right ventricle. The venous trunk, the enlarged internal mammary leading from it up over the heart and joining with the innominate vein is seen to pass directly over the heart area. The production of a murmur directly over the heart would be explained by the existence of this abnormality in the venous circulation, particularly if into this sinus was emptying a vein which coursed through the sternum.

Dissection gave one an idea at least as to the method of production of the murmur and also seemed to explain why it could be heard up toward the heart area. The well-known lesions of cirrhosis of the liver were in evidence, and there were many dilated veins in various parts of the body. The vein which contributed most to the murmur seemed to run up to the sternum and perforated a small fissure at the xiphosternal junction. Immediately beneath the sternum and xiphoid this vein could be seen to enter a large venous sinus, about 4 by 4 cm., situated in areolar tissue just under the

bone. Into the sinus, and coming directly through the diaphragm, ran another large vein, and this vein in turn could be seen to come from the suspensory ligament and to be connected with the moderately distended umbilical veins. From the upper part of this sinus there was wide open venous connection with the much dilated left internal mammary vein, and as it is highly probable that the blood current would be directed upward toward the left innominate vein and the superior cava, the murmur would tend to be transmitted over the heart and toward the great vessels. One cannot say, of course, in just what part of these venous channels the murmur would be produced: the probability is, however, that it would be where the vein entered the large sinus, for here would be the meeting of the blood currents and the general conditions which seem necessary for the production of venous sounds. With a dilatation of the trunk of the left internal mammary vein as it courses upward to penetrate the superior mediastinum on its way to the innominate, there would be opportunities for sound transmission directly over the right ventricle and auricle. One feels that in the case reported by Gambarati[7] the ability to follow the murmur upward to the episternal notch depended upon some such arrangement of venous channels. The diastole of the heart might compress these overgrown venous structures to such a degree that a diastolic lessening of sound would take place; with the heart's systole such an assumed partial obstruction might be removed. One thing would seem certain: Upon the left internal mammary vein would depend the collateral circulation of that part of the body wall directly over the pericardium.

Fig. 2 attempts to illustrate what existed in Gambarati's case and in the case of my own dissection; it probably represents more or less accurately what exists beneath the sternum and over the heart in the second case I have detailed and shows that a combination of a very common anomaly with a very usual development may quite easily give rise to confusing physical signs.

Summary. 1. Clefts in the sternum due to some defect in the process of ossification constitute a not uncommon anomaly.

2. The collateral circulation which develops in the course of cirrhosis of the liver may easily provide venous trunks which may pass through such clefts enroute to sinuses of considerable size beneath the sternum.

3. A loud murmur may be produced by the fluid eddies which will be present in such vascular connections.

4. Such murmurs, if continuous and found in the neighborhood of the third, fourth or fifth interspaces of the left side, may well be confused with those of congenital heart disease.

5. Before coming to any conclusion in connection with continuous murmurs over the heart area, finger pressure should be carefully applied to areas immediately adjacent to the sternum.

NOTE.—Hope, in his work, "A Treatise on the Diseases of the Heart and Great Vessels and on the Affections Which May be Mistaken for Them," 1832, gives, perhaps, the best description of venous murmurs, particularly those heard in the neck. Landis (Arch. Pediat., 1912, **29**, 88) gives an excellent description of these murmurs. He details well the Eustace-Smith murmur and gives as well an excellent bibliography. Blake (Clin. J., London, 1911–1912, **39** and **40**, 146 and 239) describes murmurs in congenital heart disease very like those in Cases I and II described above.

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5. Piazzi-Martini, quoted by Thayer. Piccini, quoted by Thayer. Braune, quoted by Thayer.
6. See the descriptions given by Palmer and White (*vide supra*).
7. Gambarati, quoted by Thayer (*vide supra*).

OBSERVATIONS UPON CHRONIC CHOLECYSTITIS.

WITH SPECIAL REFERENCE TO MOTOR DISTURBANCES OF THE GASTROINTESTINAL TRACT IN RELATION TO PREOPERATIVE AND POSTOPERATIVE SYMPTOMS.

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IN this paper are reported the results of a study of chronic cholecystitis with special reference to the roentgenologic technique employed and to certain factors which influence diagnosis, which cause in large measure the clinical symptoms of the disease, and which also cause the continuance of these symptoms after operation. The study is based upon an analysis of 482 cases which were diagnosed chronic cholecystitis and operated upon for this disease, and upon an end-result analysis of 666 postoperative cases. The cases in the first group are included in the cases of the second group. Neither group includes cases of acute suppurative cholecystitis nor carcinoma of the bile tract. As an attempt to correlate better the roentgenologic factors of diagnosis, chemical studies of normal and diseased gall bladders and their bile content are also reported.

Part I. The Method. The examination of the gall bladder by the older methods, in our opinion, deserves more attention than is now given to it. The history of the development of roentgenologic methods of examining the gall bladder dates from the early nineties, but it was not until 1922 that George and Leonard[1] published a procedure for the satisfactory demonstration upon plates of the diseased gall bladder. Although their work was repeated and verified in other laboratories, many investigators failed to duplicate their results. The publication of their technique brought forth no new principles; the authors merely listed the technical steps which had brought them success.

The studies herein related have for their object: (1) To investigate the truth of the assertion made by these authors that only a diseased gall bladder will produce a shadow upon the direct film; (2) to correlate the state of the gall bladder which may give such shadow upon the film and the spasm and distortion of the gastrointestinal tract; and (3) to determine, if possible, how far this correlation may aid in the recognition and differentiation of chronic gall bladder diseases. These studies, conducted over a period of several years, have led us to certain opinions and conclusions.

In order to obtain satisfactory direct films by the method of George and Leonard we find it necessary to follow rigidly certain technical details. The patient must be properly prepared by having his colon cleansed and freed of gas, if possible. For this latter purpose enemas have been found more satisfactory than cathartics, which tend to increase rather than diminish the quantity of gas present in the colon. Before films are made the patient is observed fluoroscopically and, if the colon contains sufficient gas to interfere with satisfactory films, an attempt is made to eliminate it by means of further enemas. This method of preparation is not always successful, however, for there are persons who do not tolerate enemas without resultant distention. When a satisfactory preparation by the use of enemas seems to be impossible the patient is placed for several days upon a smooth regulatory diet and is given antispasmodics. When he is ready for examination he is carefully instructed how to hold his breath and relax his muscles. This step is important, for the slightest movement of the patient will obliterate soft tissue detail. One film is then made, developed and read. Any necessary change in technique is then decided upon, for the technique must be adapted to the patient's body characteristics. In this manner six to eight films are taken, but even with this painstaking procedure satisfactory films are not always obtained.

When properly carried out, however, the above technique usually produces films that have a wealth of soft tissue detail. Indeed, this detail is sometimes confusing. One may sometimes note, in addition to the sharp margin of the liver and kidney, a number of shadows having the same size, location and contour as the shadow

of the gall bladder. Such shadows are cast, as Case 2 has emphasized, by the gastric antrum, the duodenum, the colon and other neighboring structures. However, it is easy to identify the gall bladder shadow by comparing the direct films with those taken after the oral administration of tetraiodophenolphthalein. The necessity for this comparison, however, occurs in only a small percentage of patients.

The administration of tetraiodophenolphthalein when used alone as a diagnostic procedure has, in our experience, distinct limitations. It shows obstruction of the cystic duct, either partial or complete; it frequently shows the outline of cholesterol stones; it shows distortions and irregularities of the gall bladder contour. It does not, however, reveal disease of the gall bladder wall, and its use, in consequence, may be unnecessary except when the direct films are unsatisfactory or show multiple shadows.

A factor overlooked when the method of Leonard and George is discarded is that alteration in the chemistry of the gall bladder wall, and possibly the bile content, occurs with disease, and that this chemical change may have something to do with the production of shadows on the direct Roentgen ray films. When one bases roentgenologic opinion on the Graham-Cole test alone the evidence of disease, as influenced by altered inherent chemistry, is lacking. Although the use of tetrabromphenolphthalein, and later of tetraiodophenolphthalein, has been, undoubtedly, a great aid in diagnosis, the universal employment of these dyes has distorted roentgenologic opinions. According to our observations, too much reliance is placed upon the results of their use. Our most satisfactory procedure has been to prepare films according to the older method above named, and, when occasion demands, to supplement them by the use of the Graham-Cole test. The latter test may be employed either orally or intravenously; or, in selected cases, by both methods in succession. This combined use has enabled us, in certain instances, to interpret the films of the gall bladder correctly when one method alone was inconclusive.

When the dye is administered orally the problem of intestinal absorption enters. No difference in absorption has been noted by us when the dye is given dissolved in some medium, such as grape juice, or when it is given in the form of properly prepared capsules. Nonfilling or incomplete filling of the gall bladder may be due to lack of dye absorption rather than to disease of the gall bladder itself. Satisfactory filling is, on the other hand, not infrequently found in pathologic gall bladders. In spite of the fact that the intravenous administration of the dye consumes more time and occasionally causes unpleasant reactions, it has proved, in our experience, the more satisfactory method, because the disturbing factor of intestinal absorption is removed. However, a pathologic gall bladder may give a normal response to either method.

TABLE I.—TABULATION OF PATIENTS EXAMINED FOR CHOLECYSTITIS (OCTOBER, 1922, TO OCTOBER, 1927).

	No.
Patients examined for gall bladder disease	4820
Patients diagnosed cholecystitis	1332
Patients studied and operated upon for gall bladder disease	459

These observations, as an analysis of the subjoined tables shows, are founded on the study of 4820 cases in which the gall bladder was investigated, and in which cholecystitis was diagnosed 1332 times. Of the 1332 patients in whom cholecystitis was diagnosed, 459 patients submitted to operation. The remaining 873, excepting the 23 patients tabulated (Table IV, 2) were persons who either declined surgical treatment or who seemingly did not need it.

TABLE II.—FACTORS UPON WHICH CLINICAL DIAGNOSIS IS MADE (OCTOBER, 1922, TO OCTOBER, 1927).

Clinical diagnosis made by (together with associated data):	No.	Per cent.
A. Direct evidence:		
1. + shadow	123	26.8
2. ++ shadow	185	40.3
3. ++++ shadow	109	23.7
4. No shadow and unsatisfactory	42	9.1
(*a*) Before use of dye	28	6.0
(*b*) Evidence by oral dye	3	0.6
(*c*) Evidence by intravenous dye	11	2.4
5. Direct shadow identified by:		
(*a*) Oral dye	47	
(*b*) Intravenous dye	20	
B. Indirect evidence:		
1. Motor disturbances	438	95.4
Absence of motor disturbances	21	4.6
2. Deformity of antrum or duodenum:		
(*a*) Bands	100	22.0
(*b*) Ulcers	61	13.4

In studying the films made without the use of dye (Table II) we noted varying densities of the gall bladder shadows. Shadows that were quite faint, yet plainly visible and constantly present, we graded as 1+; shadows the density of which nearly equaled the shadow cast by the liver we designated as 4+. Between these two extremes of density there were many gradations, which we grouped under the heading of 2+, and which obviously formed the largest group. Comparison of the density of the gall bladder shadow on the film with the surgeon's report as to the size of the gall bladder and thickness of the wall, was instructive. We noted that many of the cases showing 1+ shadow densities on the film were reported as having very thick walls or a viscid bile content; whereas the 4+ shadows were frequently found in gall bladders that were thin-walled and easily compressed. This observation led to the chemical analysis of the gall bladders reported here.

It is significant that in only 9.1 per cent of the cases of gall bladder disease the direct study was unsatisfactory. It will be

noted (Table II, A-4) that 6 per cent of the cases unsatisfactorily examined occurred before dye methods of study were adopted. With the advent of the use of tetraiodophenolphthalein it became possible to eliminate this group of unsatisfactory examinations. Thus in two groups of cases distinct aid was obtained from the Graham-Cole test: One in which no shadow appeared on the direct film, and in which subjective symptoms and the presence of indirect evidence made further study necessary; and one in which the multiple shadows required differentiation.

In addition to the study of the direct films of the gall bladder, observation of the opaque meal in the stomach, duodenum and colon yielded information of equal importance. In nearly 100 per cent of patients having pathologic gall bladders there was some form of motor disturbance or deformity of the gastrointestinal tract. These disturbances of function and contour assumed many forms. The most common form was spasm of the gastric antrum, the bulb, and the duodenum. Next in frequency was deformity of the gastric antrum, the bulb, or the duodenum, and less frequent was reverse peristalsis in the duodenum and fixation of the hepatic angle of the colon.

Disturbances of the normal peristaltic gradients, observed fluoroscopically, were very important findings. These disturbances were present in every case of cholecystitis studied during a period of distress. Deformity of the gastrointestinal tract observed during examination was found at operation to be due to: (1) Perivesicular inflammation; (2) congenital bands or membranes; (3) coëxistent ulcer; (4) periduodenal inflammation from pancreatitis; and (5) persistent tonic spasm. As spasm was not often found at operation, many deformities due to spasm seen on the fluoroscopic screen were not verified by the surgeon.

Stones (Table III) were demonstrated in 60.6 per cent of the cases found to have stones at operation. This percentage is about the figure given by Cole in 1915. Patency of the common duct, as evidenced by regurgitation of bárium, was seldom seen.

The first item of Table IV shows the surgeon's opinion of the gall bladder in 44 cases operated upon for abdominal disease other than that of the biliary tract. In these cases gall bladder studies had been made by us and normal findings reported. 2*a* shows an analysis of the 23 cases in which a roentgenologic diagnosis of cholecystitis was made and in which surgical opinion negatived removal of the gall bladder. Considering that of these 23 patients, 8 failed to receive postoperative relief and 1 received relief only after a subsequent removal of his gall bladder, we may draw the conclusion that our diagnoses of these cases were correct. Our percentage of correctness is then 97.1. If, however, these 9 patients represent no surgical error in diagnosis, our percentage of correctness falls to 95.2.

TABLE III.—INCIDENCE OF PANCREATITIS, STONES AND PATENT COMMON DUCT.

	No.	Per cent.
Pancreatitis	23	5.0
Stones	181	39.4 (60.6)
(*a*) Positive shadows	103	56.9
(*b*) Negative shadows	7	3.9 (60.8)
(*c*) Not found	71	39.2
Patent common duct	5	1.9

TABLE IV.—CLINICAL AND OPERATIVE FINDINGS IN THE SERIES.

		Times.
1. Gall bladder, negative Roentgen ray, negative at operation (operated for other lesions)		44
2. Gall bladder, positive Roentgen ray, negative at operation		23
2*a*. End results in 23 patients, gall bladder not removed:		
Symptoms relieved	11	
Symptoms not relieved	8	
Gall bladder subsequently removed and symptoms relieved	1	
Cases associated with ulcer	4	
Cases not traced	3	
3. Gall bladder, negative Roentgen ray, positive at operation (each case associated with duodenal ulcer)		4
4. Diagnosed chronic cholecystitis		1332
Operated upon for chronic cholecystitis		459*
5. Total gall bladder operations		459
Explored and not removed		23
		482
Per cent diagnosed correctly	95.2	97.1
Per cent diagnosed incorrectly	4.8	2.9
6. Operative deaths, 7 (459 cases)		1.5
Operative deaths, 8 (666 cases)		1.20

* 42 per cent.

TABLE V.—INFLUENCE OF DYE METHODS (JANUARY 1, 1925, TO OCTOBER 1, 1927).

	No.	Per cent.
Patients examined for gall bladder disease	2161	
Patients examined and operated upon for gall bladder disease	292	
Direct evidence alone	171	58.5
Supported by oral dye (all cases)	78	26.7
Supported by intravenous dye (all cases)	25	8.5
Unsatisfactory; diagnosis made by:		
(*a*) Oral dye	1	0.34
(*b*) Intravenous dye	11	
Unsatisfactory; no dye used	5*	
Negative; dye negative; operation positive	1	
	292	
Nonfilling by oral method; filling by intravenous method	4	
Nonfilling by oral method; nonfilling by intravenous method	4	
Oral and intravenous methods checked	3	

* 2 of which were ulcer cases.

In January, 1925, we first used cholecystography, and from that date until October, 1927 (Table V) the dye was employed in 41.4

per cent of the 292 cases later operated upon. The new technique was solely responsible for the roentgenologic opinion in only 0.4 per cent of these cases. In order to test the accuracy of the two methods of dye administration, a group of patients was given the dye by both methods, and 11 of these were operated upon. In 4 of these there was no filling after oral administration of the dye, and good filling after intravenous injection. Four showed no filling with either method and 3 showed filling with both methods.

Inorganic Chemistry of the Normal and the Pathologic Gall Bladder and Its Bile Content (R. B. Adams). At the suggestion of the authors of the present study, a series of normal gall bladders with their bile content, obtained from unembalmed bodies after accidental death, and a series of pathologic gall bladders with their content, obtained at operation from some of the cases now under discussion, were subjected to a complete inorganic chemical analysis. The autopsy material was obtained by tying and cutting the cystic duct and dissecting the gall bladder away from the liver. In each series a small section of the duct and a small section of the fundus were removed, preserved in formalin and given to the pathologist for histologic examination. The specimens were examined for evidence of gross disease and weighed, after which they were placed in a drying oven at 105° C. for seventy-two hours, dried to a constant weight, cooled and weighed again. They were then ashed in fused silica crucibles and the ash weight recorded. The ash was treated with hot aqua regia, digested for an hour, cooked, diluted and filtered through ashless filter paper to determine the insoluble gangue. There was no significant amount of the latter, however, in any case.

The filtrate was then further diluted, neutralized with NH_4OH heated to boiling and treated with an excess of NH_4OH, to determine the iron group. The latter was not subjected to further detailed analysis owing to the fact that the small amounts obtained rendered the procedure impracticable.

The filtrate was treated at the boiling point with an excess of oxalic acid, and after an hour was filtered on ashless paper to determine the calcium oxalate. Owing to the large volume of the solution, the high concentration of NH_4Cl and the small amounts obtained, it was not considered necessary to redissolve and reprecipitate this group, as error from this source would be negligible for the purpose of the present study.

The precipitation of magnesium, as magnesium phosphate, yielded in no case a weighable precipitate. No other elements or groups of elements have been reported in sufficient quantities to make them important.

In all, 10 presumably normal gall bladders and contents, obtained from autopsies, and 14 pathologic gall bladders and contents, obtained at operation, were subjected to analysis. They were all

TABLE VI.—SHOWING THE INORGANIC CHEMICAL ANALYSES OF NORMAL GALL BLADDER AND CONTENTS.

Normals.	Total wet weight.	Dry weight.	Per cent of wet weight.	Ash.	Per cent of weight.		Fe_2O_3.	Per cent of weight.		CaO.	Per cent of weight.	
					Wet.	Dry.		Wet.	Dry.		Wet.	Dry.
1.	...	8.7520	...	0.3488	...	3.98	0.1524	...	1.76	0.0020	...	0.023
2.	...	12.8380	...	0.5244	...	4.08	0.0926	...	0.72	0.0032	...	0.025
3.	...	16.2300	...	0.6482	...	4.25	0.1110	...	0.73	0.0036	...	0.024
4.	...	12.9600	...	0.2564	...	1.98	0.0454	...	0.35	0.0102	...	0.079
5.	...	21.6420	...	0.8444	...	3.89	0.2084	...	0.96	0.0028	...	0.013
6. Bladder and bile analyzed together	19.7070	8.7540	44.40	0.4204	2.250	4.81	0.0820	0.4200	0.94	0.0044	0.022	0.050
7.	24.4122	9.5632	39.10	0.4114	1.680	4.30	0.0538	0.2200	0.56	0.0022	0.009	0.023
8.	56.6038	16.4820	29.10	0.6320	1.120	3.84	0.0770	0.1400	0.47	0.0112	0.020	0.068
9.	155.2000	12.8038	8.25	1.1038	0.710	8.63	0.0990	0.0640	0.77	0.0062	0.004	0.048
10.	32.2932	10.6632	33.00	0.4544	1.410	4.25	0.1010	0.3100	0.95	0.0042	0.013	0.039
11. Bladder only	16.0140	...	...	0.0508	0.317	...	0.0068	0.0425	...	0.0028	0.017	
Total, except No. 11	288.4160	129.6882	153.90	5.6442	7.170	44.01	1.0226	1.1500	8.21	0.0550	0.068	0.392
Average, except No. 11	57.68	12.9688	30.8	0.5644	1.43	4.40	0.1023	0.2300	0.82	0.0050	0.014	0.039

Average CaO per cent dry weight for Cases 1, 2, 3, 5 and 7, 0.0216.

TABLE VII.—SHOWING THE INORGANIC CHEMICAL ANALYSES OF DISEASED GALL BLADDER AND CONTENT.

No.	Tissue.	Total net weight.	Dried at 105°C.	Per cent of wet weight.	Ash, weight, gm.	Per cent of weight.		Fe_2O_3, weight, gm.	Per cent.		CaO, weight, gm.	Per cent.		MgO.	Shadow.
						Wet.	Dry.		Wet.	Dry.		Wet.	Dry.		
10480	Bladder	5.4186	1.8556	34.30	0.0458	0.846	2.47	0.0012	0.0222	0.0650	0.0030	0.0550	0.162	Trace	4+
	Bile	18.9528	3.0918	16.30	0.2188	1.150	7.08	0.0220	0.1160	0.7120	0.0042	0.0220	0.136	Trace	
10750	Bladder	3.6446	1.1814	32.50	0.0166	0.456	1.40	0.0010	0.0270	0.0845	0.0012	0.0330	0.101	Trace	2+
	Bile*														
10518	Bladder	3.7650	0.9360	24.86	0.0266	0.707	2.84	0.0042	0.1110	0.4500	0.0012	0.0318	0.128	Trace	4+
	Bile	9.8150	0.9234	9.40	0.1042	1.060	11.30	0.0080	0.0815	0.8700	0.0018	0.0183	0.195		
10547	Bladder	6.7154	1.3128	19.57	0.0380	0.570	2.90	0.0026	0.0390	0.1980	0.0020	0.0300	0.152	Trace	4+
	Bile	21.3836	2.5078	11.70	0.2448	1.150	9.77	0.0224	0.1050	0.8930	0.0010	0.0470	0.400		
13793	Bladder and bile	47.4332	10.6372	22.40	0.5594	1.180	5.25	0.0380	0.0800	0.3560	0.0052	0.0110	0.049	Trace	2+
13719	Bladder and bile	10.4668	3.7560	35.80	0.1040	0.990	2.77	0.0028	0.0270	0.0750	0.0012	0.0120	0.032	Trace	1+
5841	Bladder and bile	20.2532	7.8426	38.70	0.2256	1.110	2.88	0.0092	0.0450	0.1170	0.0038	0.0190	0.049	Trace	2+
14041	Bladder and bile	16.9080	5.9482	35.10	0.2460	1.450	4.15	0.0296	0.1750	0.4980	0.0124	0.0730	0.209	Trace	4+
13897	Bladder and bile	11.7500	5.5800	47.50	0.1024	0.870	1.84	0.0094	0.0800	0.1680	0.0038	0.0320	0.068	Trace	2+
14128	Bladder and bile	14.9520	2.9200	19.50	0.1630	1.090	5.58	0.0098	0.0660	0.3360	0.0036	0.0240	0.123	Trace	4+
14286	Bladder and bile	52.5900	9.5400	18.10	0.6320	1.200	6.62	0.0750	0.1440	0.7960	0.0032	0.0060	0.032	Trace	2+
10041	Bladder and bile	8.3982	1.6282	19.40	0.0838	1.000	5.15	0.0040	0.0520	0.2700	0.0022	0.0260	0.135	Trace	4+
14181	Bladder and bile	11.9900	1.8600	15.50	0.0946	0.790	5.09	0.0110	0.0920	0.5920	0.0028	0.0230	0.150	Trace	4+
14150	Bladder and bile	9.7480	2.1320	21.90	0.1004	1.030	4.72	0.0040	0.0410	0.1880	0.0046	0.0470	0.216	Trace	2+

Assumed normal gall bladder and bile CaO per cent dry weight, 0.02.
Assumed 2+ gall bladder and bile CaO per cent dry weight, 0.05.
Assumed 4+ gall bladder and bile CaO per cent dry weight, 0.16.

* Duct was not tied off and bile was all in bottom of bottle.

subjected to the same procedure during the same period of time and with the same reagents and apparatus in order to have the results comparable, if not strictly accurate in all respects. The percentage of ash, etc., was calculated on both the wet and the dry-weight basis, the latter being used for comparison, as it was considered more uniform than the former. The bladder wall and the bile content separately yielded very similar percentage results, so that they were combined as a unit. The details of the analysis are given in Tables VI and VII. Cases 4, 6, 8, 9 and 10 in Table VI were arbitrarily thrown out from the presumably normal gall bladders because they were obtained from older subjects and histologic examination showed some tissue change. The series consisting of Cases 1, 2, 3, 5 and 7 yielded an average of 0.0216 per cent Ca as CaO. The average percentage of the iron group reported as Fe_2O_3 was 0.82 for the normal series and only 0.34 for the pathologic series.

Comment. For the correlation of the analytical data obtained by Dr. Adams with the gall bladder shadows obtained by us on the direct films in the pathologic series, the films were first read and the shadows recorded in terms of 1+, 2+ and 4+ density, as previously explained. With these records made, and in order to avoid biased judgment, Dr. Adams was called in to read the figures of his analyses. The results are given in Table VII. It is interesting to note that in regard to CaO the per cent dry weight averaged 0.02 for the supposedly normal gall bladders, 0.032 for the one gall bladder giving a shadow recorded as 1+, 0.05 for those giving shadows recorded as 2+ and 0.16 for those giving shadows recorded as 4+. It seems evident that as the calcium content increases, the denser becomes the shadow produced by the gall bladder on the film. We are not able at present to give an explanation for this fact, nor to ascribe any significance to it. We have been unable to reproduce, by means of various media, shadows graded as to density by using corresponding dilutions of calcium salts. The percentage of calcium content is very small in all instances, and it may be that the density of the shadow depends upon other factors than the percentage content of the calcium itself. However, this small variation in calcium content may possibly lead to a better understanding of shadow production in the future.

Part II. The Application. Our approach to the subject of chronic cholecystitis has extended over a period of nearly twenty years. During this time three noteworthy events appeared chronologically in the development of the opinions here expressed. These events were the response of persons to forced feeding under control, the publication by Alvarez[3] of the gradient theory of peristalsis, and later the development by George and Lœnard of a technique which permitted the recognition of the gall bladder upon Roentgen films.

The first came to us while correlating the principles that underlie

the reconstruction of the general asthenic body. These principles are: (1) The regulation of the gastrointestinal tract by means of diet; (2) addition of sufficient body weight by forced feeding; (3) reconstruction of the body by means of corrective exercises and general physical training; (4) establishment of a sufficient fund of body reserve strength and the fixation of a new body habit. Often while working with asthenic patients we found it impossible to regulate the bowel, and forced feeding produced repeated upsets with distress, nausea and vomiting. Gradually experience taught us that some surgical barrier, impossible to recognize, existed in the abdomen, and that when this surgical barrier was removed the bowel could be regulated and the patient could consume large amounts of food without discomfort.

The most frequent surgical barrier found in these patients was chronic disease of the gall bladder. Other lesions were peptic ulcer, chronic appendicitis, less frequently tuberculosis and rarely an irrelievable intestinal stasis. This experience led us frequently to employ the "therapeutic test" in chronic borderline abdominal cases. The patient was placed in hospital under control with heavy forced feeding. If his abdominal symptoms disappeared quickly, if his bowel became regular under the influence of the diet, and if he became more comfortable, it was concluded that he did not have local abdominal lesions of surgical import. Few mistakes were made by following this procedure and no harm came to those patients who had surgical abdominal lesions. It is to be recalled that in these earlier years, 1908 to 1914, most cases of cancer, ulcer and local kidney disease, were found by the diagnostic methods then employed and did not enter into this group of borderline cases. Moreover, at the time of the upset it was found by roentgenologic examination that spasm of the antrum, the pylorus and the duodenum, and, oftentimes, reversed peristalsis of the duodenum, were present. In two or three days' time, under the influence of an ulcer régime, the spasm disappeared, and the patient became comfortable, but an upset could be reinduced as often as heavy forced feeding was resumed. The explanation of the antral and duodenal spasm observed with the associated symptoms of gas distress, pain, nausea and vomiting, came to us in 1915 in the publication by Alvarez of his theory of intestinal gradients and of his views on the syndrome of mild reverse peristalsis. The theory of gradients explained our clinical problems so completely that, in spite of the fact that for some years other physiologists seemed loath to give credence to it, and it is still held tentatively, the theory has continued to influence more and more our clinical work in gastroenterology. We assumed that the presence of a motor disturbance at the end of the stomach indicated some form of lesion in that neighborhood, and that the diagnosis was not made until the lesion could be identified. The gradient theory offered an explanation for the "ulcer syndrome"

seen occasionally in cases of cholecystitis or appendicitis; it explained the variability of the symptoms in lesions of the digestive tract. It explained the similarity of symptoms with different lesions, and also the absence of symptoms in many cases of abdominal disease. There was no question about the existence of physiologic gradients in the heart, the digestive tract and in other hollow tubes, such as the ureter, and we felt that the time had come for clinicians to make clinical use of the theories to be derived from the presence of these gradients. In consequence, this work became the second noteworthy step in our approach to the subject of chronic cholecystitis.

The third step to the problem of chronic gall bladder disease came in the publication in 1922 of the monograph by George and Leonard on the pathologic gall bladder. Numerous articles on the roentgenologic recognition of the diseased gall bladder had been made prior to this time. Cottell (1896) and Beck (1899) had reported the ability to see stones; Rieder (1904) and, especially to be mentioned, Pfahler (1911), and later Case (1913) and Cole (1914) had all laid stress upon the so-called "indirect" evidence of gall bladder disease. But it was the work of George and Leonard that incited us to begin a systematic correlative study of both "direct" and "indirect" evidence. The indirect evidence of pressure effects and of distortions by traction appeared to us to be of less moment than the so-called reflex effects, the motor disturbances, the disturbed metabolic gradients. Cholecystography, the epochal work of Graham, Cole and Copher (1924), which now dominates the diagnostic field, has not proved so useful in our hands. It has been used only as stated above, and as reference to Tables II, IV and V indicate in detail, as a confirmatory means of recognizing the shadow of the gall bladder on the direct films in more or less doubtful instances.

Diagnosis. The diagnosis of the chronically diseased gall bladder has been made, in the course of this study, by both the direct and indirect evidence in each patient. This statement means that a distinctly clean-cut recognizable shadow of the gall bladder is sought, and usually obtained, upon the direct film, and that, at the same time, some form of motor disturbance about the end of the stomach or duodenum is seen. The latter evidence is seldom found wanting—it was absent in only 4.6 per cent. We believe it would be found in all cases if the examination were made at the time of distress. Before we made use of dye methods we were unable to obtain shadows upon the direct films in 8.4 per cent of the cases, and after we employed dye methods only 4.1 per cent depended upon the dye for recognition. It is true that the technique required for visualizing the gall bladder on direct films is more particular and the labor more arduous, but the final results—95.2 to 97.1 per cent correct diagnoses, depending upon the interpretation of item 5, Table IV—would seem to justify the added effort.

Selection of the Surgical From the Nonsurgical Case. It is obvious that with the perfection of accurate methods of recognizing the chronically diseased gall bladder, the former opinion of the surgeon that all gall bladder disease is essentially of surgical nature is not tenable. Postmortem statistics of the pathologist are well corroborated by those of the present-day roentgenologist. The diagnosis of chronic cholecystitis today cannot carry with it the expectation of surgical treatment alone. In our present series 1332 diagnoses of chronic cholecystitis were made between October, 1922, and October, 1927. Of this number, only 459 (42 per cent) underwent some kind of gall bladder operation. The remaining 58 per cent were given relief for the most part by dietetic and other measures. The temperament of the patient enters somewhat into the problem of treatment. Some persons, rather than carry on a dietetic régime, welcome an operation in the hope of obtaining immediate relief. Undoubtedly some of the 459 patients, had they so wished, might have avoided operation. On the other hand, the common dread of operation has given us the opportunity to determine whether relief of symptoms could be obtained under dietetic control in some patients who, we at first thought, should be treated surgically. In a number of patients distress was severe; in some gall stones had been recognized; yet complete relief was given by removing the motor disturbance with a smooth, regulatory diet. The patient understood that if he did not continue to obtain relief, his only recourse would be an operation. It has been interesting to note that few of these patients have returned for operation.

The segregation of the nonsurgical cases, therefore, has been made according to the functional response to dietetic control. In most instances the patient may be first given directions to carry out at home. If he is unable to obtain relief in this manner, and is able to bear the expense of two or three weeks of hospital treatment, he is placed in hospital, and his response to treatment under control is ascertained. If he obtains relief from his symptoms, and, at the same time, the spasm about the end of the stomach disappears, he is trained in the art of stomach and bowel regulation and sent home to continue the régime. If, on the other hand, he is upset; if he suffers distress from bloating; if nausea and vomiting are produced; if the antral or duodenal spasm with reversed peristalsis is increased, he is considered of necessity a surgical case, for experience has taught us to place much confidence upon this test. We feel justified, in the presence of two or three produced upsets, in giving the patient a choice between continued distress and an operation. In the years we have been testing patients in this manner we have seen the subsidence of symptoms accompany the disappearance of the motor disturbances at the end of the stomach and throughout the bowel. When the distress recurs the motor disturbances are found to be present at the same time. The two go together with

such uniformity that it is reasonable to conclude that the distress is the result of the disturbed peristalsis.

When the patient is dismissed with dietetic directions alone he is told that occasionally mild cholecystitis cases develop acute complications, as suppurative cholecystitis and secondary pancreatitis, which demand immediate care; but he is assured that the percentage of such complications is not great, and that his dietetic measures may possibly prevent them.

TABLE VIII.—POSTOPERATIVE END-RESULTS IN 603 CASES OF CHRONIC CHOLECYSTITIS AND DURATION OF SYMPTOMS IN THE BROAD- AND ASTHENIC-BUILT PATIENT.

		Broad.		Asthenic.	
	No.	No.	Per cent.	No.	Per cent.
Practically free immediately	133*	119	28.0	14	8.0
One or two relapses	14	9	2.0	5	3.0
Duration:					
1 month	4	3	1.0	1	0.5
2 to 3 months	21	16	4.0	5	3.0
4 to 6 "	44	32	7.5	12	7.0
1 year	42	29	7.0	13	7.5
1 to 2 years	16	10	2.0	6	3.5
2 years and over	64	41	9.5	23	13.0
Symptoms:					
Continuous	25	16	4.0	9	5.0
Periodic	116	75	17.5	41	23.0
Mild, less than before operation	83	55	12.5	28	16.0
Severe, equal to or greater than before operation	41†	25	5.0	16	9.0
Total	603	430	71.3	173	28.7

* 22 per cent (78 per cent).
† 7 per cent.

Postoperative Medical Treatment. As with the preoperative case of mild chronic cholecystitis, so with the case operated upon, the presence or absence of continued or periodic distress depends for the most part upon the presence or absence of motor disturbances of the gastrointestinal tract. Table VIII gives a postoperative end-result analysis of 603 cases. Only 22 per cent of the patients were relieved of the distress for which they were operated upon within the period of surgical convalescence. Seventy-eight per cent continued to have distress of variable intensity over periods of time ranging from a month to more than two years. With some patients the symptoms were more severe and more persistent than before operation. Most of the latter group were returned to the medical hospital for subsequent treatment, some patients as many as three or four times, before relief became permanent. Two factors seemed to be of importance in bringing about ultimate relief, the first being freedom from motor disturbances, as already described, and the second the associated influence of a general asthenic state. Although chronic gall bladder disease is much more prevalent in persons of

the broad or sthenic type of build—71.3 per cent in the series as compared with 28.7 per cent in persons of asthenic build—yet the relief of symptoms on the whole in the patient of broad build is quicker and more complete than in the one of narrow build. Of the broad-built, 28 per cent received immediate relief, whereas of the asthenic-built, only 8 per cent received like results. Many of the asthenic-built patients had to be reconstructed according to the four principles enumerated above before relief was obtained. But oftentimes in the broad-built patient, as well, gymnasium work, horseback riding, etc., played an important rôle in the ultimate cure.

In the study of surgically treated patients under control in hospital we noted the same relationship between the presence of motor disturbances of the stomach and duodenum and the presence of symptoms as were found in patients not operated upon. The absence of symptoms seemed to accompany at all times the absence of antral and duodenal spasm. In the exceptional case in which relief was not obtained subsequent operation revealed the presence of an overlooked stone. Adhesions about the duodenum and surrounding viscera played no part in the postoperative failure in this series of cases. Distinct secondary pancreatitis was recognized only 23 times in 459 cases (5 per cent), a percentage lower than in most similar statistics. We have found no reason to agree with Bassler*, however, when he states that the pancreatic function is disturbed in most gall bladder diseases—67 per cent in his experience—and we have found no instance in which distinct fat stools followed the ingestion of fat in the diet, as reported by Else,[5] or in which we could satisfy ourselves that the postoperative symptoms, as believed by Bassler, were related to pancreatic hypofunction.

The postoperative medical treatment has consisted, therefore, of the same dietetic methods of control and of the application of the same general reconstruction principles employed in those patients who found relief from symptoms without the assistance of surgery. The patient who contemplates an operation is told frankly that he must expect more or less distress to remain for a time after operation, but that he can be eventually relieved by following the above régime. By this postoperative control of the patient have we justified, in our own minds, the increased amount of gall bladder surgery which the newer methods of diagnosis have brought about, and the many apparent postoperative failures have been given a new understanding. The diseased gall bladder is considered, by reason of the local symptoms, a local barrier, which, in certain instances, must be removed in order to remove disturbances of peristalsis.

* Dr. A. H. Aaron reported, before the American Gastroenterologic Association, May 6, 1929, observations on the enzymatic concentration in the duodenal contents in a group of 50 cases over a period of three years. The gall bladder cases showed but little variation from normal figures both before and after cholecystectomy.

In 63 cases of combined cholecystitis and peptic ulcer (Table IX) the same principles of postoperative treatment have been followed. A greater number of patients obtaining immediate relief from operation is noted in this series than in the series of uncomplicated cholecystitis. The cause of this result is not apparent. Possibly the ulcer is the dominant lesion and operation for the ulcer removes the opportunity for recurring spasm. Spasm, however, is by no means removed in all cases, and the ultimate recovery of the patients of this group has not been uniformly as good as that of the patients with uncomplicated cholecystitis. In this series of patients, likewise, the influence of the constitutional factor is noted as it was in the other series.

TABLE IX.—POSTOPERATIVE END-RESULTS IN 63 CASES OF CHRONIC CHOLECYSTITIS AND ULCER, SHOWING DURATION OF SYMPTOMS IN THE BROAD- AND ASTHENIC-BUILT PATIENT.

	Total	Broad.		Asthenic.	
		No.	Per cent.	No.	Per cent.
Practically free immediately	30	22	55.0	8	35.0
One or two relapses	2	2	5.0		
Duration:					
1 month					
2 to 3 months					
4 to 6 "	1	1	2.5		
1 year	7	3	7.5	4	17.0
1 to 2 years	3	2	5.0	1	4.0
2 years and over	3	1	2.5	2	8.5
Symptoms:					
Continuous	4	2	5.0	2	8.5
Periodic	6	4	10.0	2	8.5
Mild, less than before operation	6	3	7.5	3	13.0
Severe, equal to or greater than before operation	1	..	..	1	4.5
Total	63	40	63.5	23	36.5

To the usual two weeks' postoperative surgical treatment we have advised all patients operated upon to add a week or ten days of dietetic training in the medical hospital. As not all patients, for financial or other reasons, have done so, we have observed, by comparison, quicker convalescence and greater freedom from distress in the patients so trained.

Causes of Operative Failure. It is evident from what has been said in the foregoing paragraphs that, in the present series of cases under discussion, the only important cause for an operative failure of relief of symptoms has been the continued motor disturbance along the gastrointestinal tract. Into this problem of disturbed peristaltic gradients a general asthenic state has many times entered. Relief of the one and reconstruction of the other has led finally to good postoperative end results. In 2 cases an overlooked common duct stone led to reoperation. Adhesions between surrounding viscera and the gall bladder, or its former site, produce for the most

part reflex disturbances of peristalsis—disturbances which are functional in character, and can, in consequence, be relieved. Only rarely do adhesions in the upper abdomen become obstructive in character. Hepatitis may have existed, in greater or less degree, in all of the cases. In certain cases associated with a fixed secondary or a borderline anemia, sections removed from the liver for histologic and bacteriologic study showed the presence of chronic infection. In two or three instances of apparently progressing chronic obstructive biliary cirrhosis the patients have remained in poor health. The use of the "therapeutic test" has been of distinct value in some of our postoperative cases in showing that relief of symptoms was possible and that the actual surgical barrier had been removed.

Summary. 1. A clinical study of a considerable number of cases of chronic cholecystitis has been made for the purpose of correlating the "direct" and the "indirect" evidence of the presence of gall bladder disease. It has been shown that the proper correlation of these factors leads to a remarkably accurate clinical diagnosis of gall bladder disease—95 to 97 per cent correct diagnoses.

2. A method is given by which, with a high degree of safety, cases of chronic cholecystitis which should be considered surgical in type may be segregated.

3. Based upon the metabolic gradient theory of peristalsis, a logical explanation is given for the presence of most of the preoperative symptoms of chronic cholecystitis and also for the presence of the same symptoms remaining after operation. A workable method of postoperative medical treatment, based upon this theory of peristalsis and upon the constitutional type of the patient, is also given.

4. The CaO content of the gall bladder wall increases in percentage, for some unknown reason, as the gall bladder increases the density of its shadow upon direct Roentgen films. The content varies from an average of 0.02 per cent CaO dry weight in presumably normal gall bladders, which cast no shadow upon the direct film to an average of 0.16 per cent CaO dry weight in those gall bladders which cast a dense shadow upon the direct film. No explanation is given for this finding, and its relation, if any, to shadow production on the direct film has not been determined.

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A CLINICAL STUDY OF VISCEROPTOSIS.

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Glénard's description of the visceral ptoses in 1885 has been followed by many articles on that subject. A number of them have added to our knowledge; those of Goldthwaite[1] and White[2] dealing with the orthopedic element in visceroptosis being especially interesting. It appears to the writer that none of the articles, whether in textbooks or in journals, gives adequate consideration to this condition, as one gains the impression from them that visceroptosis is merely a manifestation of a general constitutional weakness and is of little significance. The character of the symptoms ptosis may cause, the similarity which the symptoms may bear to those of organic disease, and the effect of ptosis upon the efficiency of the individual are not emphasized. It is for this reason that we shall attempt a discussion of visceroptosis.

Prior to the discovery of the Roentgen ray the position of the viscera was determined by studying their relationship in the cadaver. The use of the Roentgen ray in studying the skeleton, body cavities, and viscera in the human being has given much information concerning the relationship between the size, position, and motility of the viscera to body form. As a result of these studies we have learned that there are variations from the theoretically normal body previously described, and from this information we have deduced specifications of certain general body types which may be regarded as normal. The physician who is interested in form, and who recognizes that form and function are different phases of the same vital process, can appreciate the differences existing in persons of various body types. The lack of appreciation of these differences in types is the cause of the failure of many therapeutic measures.

In 1917 Mills,[3] in submitting a classification of body types, described the sthenic and the asthenic as the dominant ones. According to this classification, the sthenic group is characterized by a thick, broad, short thorax, a long abdomen of great breadth in the upper portion, and a relatively small pelvis, padded with fat. The asthenic group is characterized by frailty of build, a long, narrow thin chest, a short thin abdomen, and a relatively wide and capacious pelvis. To these groups Mills added the hyperstenic and hypoasthenic subdivisions. We adopted this classification and have found a fairly constant relationship between body type and the size, position and motility of the viscera. For example, a thorax or abdomen with certain anatomic characteristics can, of necessity, accommodate organs of certain form and in certain positions. Under

the fluoroscope the stomach of both the sthenic and the hypersthenic person is seen lying well above the interiliac line; while in the asthenic and hypoasthenic person, all of the organs are low with either the stomach or the transverse colon, and frequently both, lying in the pelvis. Changes in the rate of peristalsis also are often observed in the latter group.

The body habitus must be considered before a diagnosis of ptosis can be made. For instance, if in a sthenic person the lowest point of the greater curvature of the stomach is below the interiliac line; or if the transverse colon lies in the pelvis, we consider the position of those organs to be below the normal level for that type. Studies of the asthenic type confirm the belief that only with a considerable elongation of the stomach—the greater curvature lying well below the line between the iliac crests, or the transverse colon lying low in the pelvis—is a diagnosis of ptosis permissible. With these arbitrary rules in mind, we have approached this study of visceroptosis.

In order to understand the causes of ptosis, it is necessary to consider the anatomic factors concerned in maintaining the position of the viscera; for deviations from the normal create certain mechanical difficulties under which the gastrointestinal tract must work. The intestinal tract is held in position by: (1) The mesenteric attachments; (2) intraäbdominal fat; (3) intraäbdominal pressure and (4) the shape of the abdomen.

1. The mesenteric attachments: The intestinal tract, beginning at the second portion of the duodenum, is attached to the abdominal wall by the mesentery throughout its entire length. Since the large intestine is found more frequently to be abnormal in size and position, we shall speak only of the mesocolon. The ascending and descending colon and the hepatic and splenic flexures are attached to the posterior abdominal wall by the mesentery. The mesentery to the transverse colon is a thin, feebly supporting membrane. Coffey[4] points out that failure of the right mesocolon to fuse properly with the parietal peritoneum predisposes to abnormal mobility of the cecum. In Waugh's[5] opinion the abnormal mobility of the cecum and ascending colon leads to inefficient function and failure of peristalsis in that portion of the intestinal tract. Coffey also points out that the failure of the omental bursa to become obliterated weakens the feeble support of the transverse colon and more easily permits ptosis.

Probably the importance of the mesentery in supporting the weight of the bowel is less than its importance as a medium through which the nerves, blood and lymph vessels pass to the intestine. When excessive tension is imposed upon the mesentery by ptosis of the viscera, disturbances in the circulation of the blood are likely to result, the effect of which may be mild or sufficient to alter the circulation throughout the body.

2. Intraäbdominal fat aids in the support of the gastrointestinal tract by acting as a cushion for the viscera and by increasing intra-abdominal pressure. Deposits of fat in the pelvis diminish the capacity of the lower abdominal cavity, and when the fat is absorbed a sagging of the viscera will take place.

3. Intraäbdominal pressure is a negative pressure existing between the gastrointestinal tract and the osseomuscular walls. Wagoner's[6] studies on this subject are of special interest as they show the effect of intraäbdominal pressure on the function of the stomach and intestines. He measured the intraäbdominal pressure in animals and in cadavers and found the pressure normally to vary from about −4 to −20 mm. of water. When he placed the experimental subjects in the upright position, the size of the abdominal cavity increased and the viscera gravitated to a lower level in proportion to the degree of emaciation and the relaxation of the abdominal muscles. As the cavity enlarged, the pressure within the abdomen increased tenfold in some of the animals while it increased from −20 to −106 mm. of water in the cadavers, the average increase being −52. Wagoner[7] found also by experiment that peristalsis is in a large measure dependent upon the relation between the pressure within the abdomen and the pressure within the intestine. For example, changes in intraäbdominal pressure to a greater negativity resulted in a gradual diminution of peristaltic contractions. As the pressure in the dog exceeded −50 mm. of water, there was a gradual diminution in peristalsis until there was obliteration of all movement. If the intraäbdominal pressure could be measured in visceroptotic patients, probably we would find that it often exceeds −50 mm. of water, and in the light of Wagoner's experiments we may expect peristalsis to be diminished in proportion to the increase in this pressure. A diminution in the rate of peristalsis promotes stasis of the intestinal contents, and sagging of the bowel, with a loss of tone of the involuntary muscles.

4. The shape of the abdominal cavity largely determines the position of the viscera. It is greatly influenced by the tone of the voluntary muscles, and the tone of the muscles is influenced by posture. The sthenic person has an erect posture; the tone of the abdominal muscles is good, and the viscera occupy mostly the upper abdomen. The asthenic person assumes a passive or stooped posture; the upper abdomen is often constricted; the distance from the umbilicus to the ensiform process is greater than the distance from the umbilicus to the side of the abdomen, and the abdominal muscles are relaxed. This relaxation increases the size of the lower abdominal cavity; causing the viscera to descend to a lower level when the individual stands.

There are two types of visceroptosis, the congenital and the acquired. The majority of the cases are congenital. An inherent structural weakness predisposes to ptosis which may be accentuated

by a long, slender body, relaxed tissues, failure of the right mesocolon to fuse with the parietal peritoneum, or of the omental bursa to become obliterated, poor muscular development, flattening of the lumbosacral curve, and faulty posture. As a result of the faulty posture and the deviations from the natural curves in the vertebral column the weight-bearing centers shift from their normal positions. Ptosis may be found also in patients with a more perfect body shape and posture. It may then be due either to a relaxation of the abdominal wall ensuing upon a debilitating sickness, poor habits, childbirth, to any condition causing prolonged strain upon the abdominal muscles, or to a developmental defect in the mesocolon.

Visceroptosis is encountered by the general practitioner, the internist, the surgeon, the orthopedist, and the obstetrician. There are three groups of persons with ptosis: First, those who have ptosis but who do not have symptoms; second, those who have ptosis and in addition have an organic lesion; third, those who have ptosis and whose symptoms are due to the prolapsed viscera.

Clinical Investigations. During the past two years we examined 37 patients whose symptoms were found to be due to visceroptosis. In that period also we examined a number of other patients who had, in addition to ptosis, an organic lesion in the gall bladder or some portion of the gastrointestinal tract. Some of these patients had symptoms due to the ptosis, but as the organic lesions were of primary importance, those patients were not considered in this study.

In the 37 patients we found ptosis of the stomach in 31; of the transverse colon in 26; of both the stomach and colon in 24; and a movable right kidney in 3. Nineteen of the patients were males; 18 were females, 8 of whom had borne children. The body weight of 28 patients was below normal for the age and sex. In 20 of the patients the ptosis was considered to be of congenital origin, and in 8 patients acquired. It was difficult to decide whether the ptosis was congenital or acquired in the remaining 9 patients since from the anthropometric examination they might have belonged to both the congenital and acquired classes. Each of the 9 patients was well proportioned, and it is possible that the prolapse of the viscera resulted from faulty posture or from prolonged physical strain. On the other hand, in 5 of these patients with a rather long decubitus we could see an approach to the slender type which may have predisposed to ptosis. The following table shows the age incidence:

TABLE I.—AGE INCIDENCE.

Years.	No. cases.
10 to 20	2
20 to 30	15
30 to 40	12
40 to 50	7
50 to 60	1

Gastrointestinal Symptoms and Findings. All of the patients had had "indigestion" for a period of a few months to several years; the average duration of symptoms was two years and ten months. The early gastrointestinal symptoms were few, consisting mainly of fullness after meals, flatulency and lethargy. As the abdominal muscles relaxed and the negative pressure within the abdomen increased, the motility of the gastrointestinal tract diminished in proportion to the increase in the negative pressure, as might have been expected from Wagoner's experiments mentioned above, the symptoms grew in number and became more generalized. There were variations in the symptoms depending upon the organ prolapsed, yet certain ones were common to all, such as a feeling of weight in the lower abdomen, a dragging sensation and backache, all of which were relieved by lying down. In addition to these sensations a number of patients complained of more or less constant pains in some region of the abdomen. The pain was in the lower right quadrant in 11 cases; under the left costal border in 7; in the upper right quadrant in 5; and in the center of the abdomen in 3 cases. The characteristics of the pains were: Irregularity of appearance during the day, and constancy in type in the individual cases. Conspicuous among the symptoms, especially in those patients with a low stomach, was a sensation of epigastric burning, which was relieved by food. When examined fluoroscopically the stomach often showed hyperperistalsis or hypoperistalsis; and frequently there was evidence of stasis in the colon, such as a delay in the passage of the opaque meal. Twenty-three patients complained of constipation, and in all of these the transverse colon was found, fluoroscopically, to be lying low in the pelvis.

Twelve patients showed normal acidity of the gastric secretion; 3 cases showed a mild hyperacidity; 5 showed an achylia; and in 3 of the patients with either hypoacidity or achylia, a dilatation of the second part of the duodenum was found. A mobile cecum with tenderness on palpation was noted in 14 patients.

Constitutional Symptoms. Symptoms such as drowsiness, dizziness, fainty sensations, dull headaches and inability to perform the day's work without feeling the need of rest were present in the majority of the patients. Mental and physical fatigue were prominent symptoms in the 14 patients who exhibited a systolic blood pressure of 110 or less. Five of the patients with hypotension showed also a postural hypotension, the systolic pressure falling from 6 to 12 mm. after they had stood for three minutes. This phenomenon may be explained by the accumulation of blood in the splanchnic vessels, particularly in the veins. The stasis of the blood probably accounts partly for the heavy, dragging sensation in the abdomen. The skin and mucous membranes presented an anemic appearance in the majority of patients with visceroptosis, though the erythrocyte count and hemoglobin content were moderately reduced in only fifteen.

Fourteen patients presented symptoms suggesting disturbances in the basal metabolic rate, which was found to be normal in 5; slightly increased in 5; while in 4 patients it ranged from −10 to −16. The patient in whom the reading of −16 was obtained showed a marked gastroenteroptosis and delayed emptying time of the stomach on Roentgen ray examination. This patient, an unmarried girl, aged twenty-four years, ceased to menstruate two years previously and showed other evidences of endocrine disturbance, such as a moderate deposition of fat on the hips, but all of her symptoms were gastrointestinal. The clinical picture was that of myasthenia gastrica. In this case the visceroptosis was not the cause of the endocrine disturbance, though the latter was no doubt a factor in causing slow peristalsis.

Nervous Symptoms. Those patients whose symptoms were of a few years' duration often gave the impression of being neurotics or hypochondriacs. It is an easy matter for such persons to develop an introspective attitude as they usually worry easily. When their symptoms of "indigestion" and their "weak spells" continue after various remedies have been tried, they regard their symptoms seriously and the nervous element may eventually dominate the clinical picture. In some cases the inherent and allied deficiencies of the abdomen and central nervous system are manifested simultaneously; in others one of them predominates, and if absorption of toxic substances as a result of constipation are superimposed it is not difficult to imagine far-reaching results on an already unstable central nervous system.

Case Abstract. Six months ago an asthenic middle-aged woman came to the office complaining of "poor health and nervousness," which began eight years previously. During the first three years these symptoms were worse at intervals of two or three months, but were improved by a few days' rest in bed. In the past five years she had gradually grown weaker; the constipation had become more severe; the nervousness had increased; she was conscious of a dragging sensation in the abdomen; in fact, she felt "heavy all over" when standing or walking. In the past year she has not enjoyed her food as it caused her to feel "full and heavy;" she has been nauseated; she has been more nervous, and she was in bed fifteen weeks prior to the examination. She was discouraged because all methods of treatment had failed, including chiropractic adjustments.

Physical examination revealed relaxed abdominal muscles, evidences of visceroptosis, and a mobile cecum with tenderness on palpation. The Roentgen ray showed the greater curvature of the stomach lying 3 inches below the iliac crests and the transverse colon low in the pelvis. Gastric analysis showed achlorhydria, but other laboratory examinations, including the basal metabolic reading, were normal. She was treated for ptosis in the ways to be mentioned later, and improvement in all symptoms was noted in a few weeks, and within two months the patient was in better health and spirits than she had been for eight years.

It is not our intention to prove that visceroptosis is the cause of the vast number of symptoms of which a patient may complain.

Although visceroptosis cannot be considered pathologic in asthenic persons, yet many of them later will have symptoms of perverted physiology when the gastrointestinal musculature becomes atonic. However, ptosis of one or more viscera in a sthenic person may be regarded as pathologic. In either instance ptosis is often disregarded and the patient becomes a chronic complainer or has been one for a period of time.

Moody[8] endeavored to determine the normal position of the abdominal viscera in persons of different types by Roentgen raying the gastrointestinal tract of 1000 university students. He found one or more viscera low in a large percentage of his subjects and he concluded that the diagnosis of enteroptosis, gastroptosis, and coloptosis are seldom or never justifiable. It should be remembered that his observations were made at the time of life when ptosis rarely causes symptoms. It would be interesting to learn the condition of those individuals ten or fifteen years later, when the strain and stress of life have taxed them. We believe a diagnosis of enteroptosis, gastroptosis, or coloptosis is justifiable since each denotes a specific relationship of the viscera to the body habitus.

Diagnosis. The points of distinction which should be stressed are: 1. The history of duration of the symptoms for months or years. During that time the symptoms have been persistent but not severe, whereas, organic lesions usually progress and the symptoms become correspondingly more severe.

2. Short intervals of a few days to two or three weeks of comfort after the symptoms have appeared as compared with longer intervals when the gall bladder or appendix is diseased.

3. The absence of the characteristic periodicity of the symptoms of duodenal ulcer.

It is rarely difficult to make a diagnosis of ptosis, though it is sometimes difficult to say a patient does not have an organic lesion. Radiologic examination renders valuable assistance in differentiating the conditions.

Treatment. Since the manifestations of visceroptosis are not always confined to the abdomen but are often protean in nature, it is necessary to recognize the general derangement from which the patient may be suffering if the treatment is to be successful. The treatment should be directed toward restoring the prolapsed organs to their normal position as far as possible, and to improve the general condition of the patient.

Patients with visceroptosis need an abdominal support, especially in the first few months of treatment. A large number of supports have been devised; some of them serve the purpose satisfactorily while many others are useless or harmful. The support should be fitted by a person who has both a knowledge of the anatomy of the abdomen and the object to be attained by the wearing of a support. It should be simply constructed of firm material, easily adjusted

and retained in position, and it should lift the lower abdomen. The support which accomplishes this purpose relieves the heavy dragging sensations in the abdomen by diminishing the tension on the mesentery and the intestines. It also relieves the backache. It is always well to see fluoroscopically if the support is holding the stomach and transverse colon in better position. Minor adjustments are often necessary. In the occasional patient when a well-fitting binder does not give the proper support, a change to another make will often have the desired effect. Many of the patients must continue wearing the support, while others may discard it in a few months, especially if they have gained weight and the tone of the abdominal muscles has increased under the influence of exercises and posture.

The orthopedic element of the treatment of visceroptosis consists in a process of reëducation of the individual that will lead to the assumption of a posture different from his habitual one. With a knowledge of body mechanics we can help him maintain the best and easiest posture that will strengthen the muscles. The assumption of the active posture will change the weight-bearing centers in the vertebral column to their normal position, and tension will be put upon the abdominal muscles. This will accomplish more in the treatment of ptosis than merely the prescribing of an abdominal support and corrective exercises. Corrective exercises, however, are indicated for increasing the expansion of the thorax and upper abdomen and at the same time increasing the tone of the abdominal muscles. They will also increase the strength of the spinal muscles.

In conjunction with the abdominal support and physical education, a few drugs are necessary for many of the patients. Dilute hydrochloric acid should be given to those who have a low acid secretion. Occasionally an alkaline powder will allay the sensitive gastric mucosa in the patients with a tendency to high acid secretion; and belladonna is indicated when any portion of the intestinal tract is irritable or spastic. Constipation should be overcome but purgatives should be avoided as far as possible. The bowels can be regulated usually by taking of mineral oil with the addition of agar if necessary. When constipation is not severe many patients will not require the oil except at intervals, after the first month or two of treatment. When constipation is intense, as it is in a number of these patients, we have found that small doses of aromatic cascara combined with iron and calcium lactophosphate will give excellent results. Later a combination of mineral oil and agar, or milk of magnesia will be sufficient. Ultimately, all laxatives should be omitted, if possible. Occasionally a mild sedative is necessary to quiet the irritable nervous system. Iron and arsenic are beneficial in stimulating the appetite in those patients who have little desire for food, and will also increase the erythrocytes and hemoglobin when an anemia is present.

A generous diet should be prescribed. It is a wiser policy for the patient to take four or five small meals during the day to avoid distending the stomach with large quantities of food. Cod-liver oil contributes splendidly toward upbuilding. As the weight increases, deposits of fat in the abdominal wall aid in supporting the viscera; the patient acquires a sense of well-being; and he is less easily fatigued.

Rest in the recumbent position is an important feature in the treatment. It relieves the tension on the mesentery and facilitates the movement of the gastrointestinal contents. The patient should lie down for thirty to forty-five minutes after each meal.

It is necessary that the patient continue the treatment. Even if, after a few months, the patient is able to do without the support and the drugs, he should continue the regimen of health-forming habits—correct posture, exercises, a rational diet, and rest. If he does not persist in carrying out these measures, the symptoms will recur.

Results of Treatment. It is interesting to observe the results of treatment in this series of cases. There was improvement in the gastrointestinal symptoms in all the patients though several of them complained of fullness and lassitude occasionally after meals. However, neither was as marked as before treatment. The dragging sensations in the abdomen with backache disappeared. The pain disappeared in 21 out of 26 patients, while in the remaining 5 it seemed to occur with an accumulation of gas and was referred to more as a dull aching sensation in the same region of the abdomen in which it formerly occurred.

In 10 of the patients with hypotension the systolic blood pressure increased from 4 to 22 mm. of mercury, and in 3 of those with postural hypotension the systolic pressure increased from 8 to 20 mm. There were variations in the systolic readings on subsequent observations of each patient. Some clinicians have reported that ephedrin increases the blood pressure. This drug was prescribed in 6 cases but we did not find that it raised the pressure above the level it had reached as a result of the treatment of the ptosis.

In 7 of the patients the nervous symptoms were prominent, and in all of them there was improvement although it was slower than the improvement noted in the other symptoms. Some of these patients complained of nervousness at irregular intervals but in only one was it as pronounced as before treatment. That patient, a man twenty-eight years of age, was susceptible to nicotine and he suffered from nervousness after smoking.

Coincident with improvement in the symptoms all of the patients gained weight, and experienced less mental and physical fatigue upon exertion. After a few months 12 patients discontinued treatment on account of feeling well. Their symptoms recurred but they improved quickly upon the reëstablishment of treatment. Such

chronic infections as ethmoiditis, cervicitis and prostatitis were found in a few of the patients and were treated conservatively. Tonsillectomy was advised in 2 of 11 patients in whom infected tonsils were found.

Conclusions. 1. Roentgen ray studies of individuals have shown that there is a fairly constant relationship between the size, position and motility of the viscera and the body type. The two main types, the sthenic and asthenic with their subdivisions, the hyperstenic and the hypoasthenic, must be recognized, and the approximate normal level of the viscera in each type must be borne in mind before we can say that ptosis exists.

2. Visceroptosis is usually found in the asthenic person who has an inherent structural weakness; a faulty posture; relaxed muscles; and whose normal weight-bearing centers have shifted. There may be also an incomplete fusion of the right mesocolon or failure of the omental bursa to become obliterated. These defects are conducive to a downward displacement of the viscera. Ptosis occurs less frequently in the sthenic individual and is due to prolonged strain upon the abdominal muscles or to failure of the mesentery to develop properly.

3. Persons with ptosis may or may not have symptoms. They will develop symptoms when the intraäbdominal pressure increases to a greater negativity, thus diminishing the peristaltic contractions in segments.

4. A study of the symptoms of 37 patients with ptosis shows that gastrointestinal symptoms are common to all, and that there may be symptoms referable to the circulatory system, especially when hypotension exists. A varying degree of disability was imposed upon the patients, especially upon those in whom hypotension was found. The sex incidence in this series is unusual in that males rather than females predominated.

5. This study shows that the symptoms of visceroptosis may simulate those of duodenal ulcer, chronic appendicitis and chronic cholecystitis. There are differences in the history that give a clue whether the symptoms are due to prolapse of the viscera or to organic disease. On physical examination we find certain characteristics that differentiate visceroptosis from other conditions. It is not difficult to determine the presence of ptosis, though it is sometimes difficult to say that organic disease does not exist. Roentgen ray examinations are valuable in the differentiation. Even when an Roentgen ray examination is not necessary it is desirable to have it made in order to determine the exact position of the stomach and colon.

6. Visceroptosis is not usually a disease, though it is often the cause of perverted physiology. Ptosis of one or more viscera in a sthenic person may be considered pathologic.

7. A diagnosis of enteroptosis, gastroptosis and coloptosis is justifiable as it denotes a certain anatomic topographic condition.

8. The treatment of visceroptosis should be directed toward returning the viscera to their normal position and improving the general condition of the patient.

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OBSERVATIONS ON VISCERAL PAIN.*

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Pain in connection with visceral disease is an only too common complaint, and a large part of the practitioner's daily work consists in its diagnosis and treatment. What organ is at fault? What is the cause of the disturbance? Is the pain felt in the viscus under suspicion, or is it referred to superficial structures? Such questions are ever in his mind and the answers to them largely govern his conduct of the case.

At first glance it seems almost too evident for discussion that many pains are really felt in the organs in which the disturbance exists, and yet since the time of Haller, 1763, there have been many who have doubted this and say that there is no true visceral pain. Lennander[1] thought that all such pains were due to inflammation of, or pressure or traction on, the parietal peritoneum and its sub-

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serous layer, and therefore were somatic. Others believe that the pains are really referred from insensitive viscera and are felt in the parietal structures supplied by the cerebrospinal nerves which belong to the spinal segments to which the splanchnic nerves of the involved organs run. Such was the view of Sir James Mackenzie, who wrote, "Pains arising from the viscera are not felt in the organ, but are referred to the peripheral distribution of cerebrospinal nerves in the external body wall."[3] Sir Henry Head endorses the referred nature of much pain in visceral disease, but adds, "I do not mean to state that pain is never felt in the organ affected. Far from it. The pain is frequently felt in the organ itself, but it is dull, heavy, wearing, and not sharp, aching, stabbing, like the referred pain."[4]

Those who do not believe in true visceral pain point to the fact that the viscera may be handled, burnt, pinched and in many ways physically insulted without much pain resulting. Recent work, however, has shown that this is only partially true. Thus C. H. Mayo wrote last year, "It can be shown that the structures in the abdomen are sensitive to pulling, clamping and tying."[5] Hurst, who believes in visceral pain, says that the stimulus must be adequate, and that the only adequate stimulus is tension in the damaged organ. It is well known that the sensory nerve endings in the viscera are few in number, but they are present,[16] and we must remember that although a normal tissue may have little sensation of pain, an inflamed one can be acutely sensitive. This point was emphasized by A. Primrose several years ago.[7]

Most will probably agree with Sir E. Farquhar Buzzard when he wrote, "Splanchnic pain is something very real, at any rate to anyone who has experienced the tortures of colic."[9]

But the question of whether or not true pain exists in a viscus is not the one in which we are especially interested here, but rather in the fact, admitted by most, that when some irritation occurs in an internal organ there is often pain with tenderness and muscular rigidity present in that part of the parietes which is innervated from the same spinal segment as receives the visceral nerves from the affected organ. This so-called "referred pain" may be only a slight part of the suffering which to the patient seems to be internal, or it may be the chief complaint and according to some the whole source of the distress. Ryle, who believes in the frequency of true visceral pain, thinks that when pain is referred it is usually evidence of inflammation of an organ. He concludes, "Non-inflammatory visceral pain, for example, intestinal colic, must be very severe before any somatic pain accompanies it."[12] In angina pectoris there is no inflammation of a viscus and yet terribly severe referred pain is often present.

It seems that some kinds of visceral irritation produce only referred pain and others apparently only true visceral pain, while in many both exist.

A common explanation of referred pain is that the afferent impulses from the irritated tissue on reaching the central nervous system spread to adjacent sensory centers and so excite these that painful impulses from them reach consciousness and are interpreted by the brain as coming from the peripheral distribution of such nerves. Thus when one has an inflamed tooth the pain may be felt not only in the tooth but also in the side of the face or in the ear. This is very clear when we are dealing with somatic nerves, but the same explanation is used when the afferent impulses must pass through the involuntary nerves and then spread and excite adjacent cerebrospinal cells. Thus in the case of irritation of the gall bladder pain may be felt in the parietes supplied by the eighth and ninth dorsal nerves; in angina pectoris in the distribution of the first to the fourth dorsal nerves, and so on. Such an explanation of the mechanism of referred pain is a very conceivable one anatomically when the whole course is somatic; and when the afferent portion is visceral we may recall the close connection which exists between the vegetative afferent nerves and the somatic, both in the posterior root ganglia[15] and in the gray matter of the cord.[16]

But a difficulty arises, and it is with this difficulty that we are here concerned. If the superficial pain is referred, that is, if it is really due to excitation of the central cells and is only interpreted by the mistaken brain as coming from the peripheral distribution of that somatic neuron, any cutting or damaging of the nerves distal to the center should make no difference. The pain should still be felt as in the parietes, it only having been "projected there by the mind." (Lange.) But the experience of every physician as also of the laity is that when an anodyne application is made to an area of referred pain it tends to lessen it. Hilton had noted this and in 1863 wrote, "These superficial pains, although depending upon a remote cause, may sometimes be relieved by local anesthetics, as prussic acid, hemlock, belladonna and opium."[17]

In 1926 Lemaire published a paper[18] on the relief of referred pain by infiltration of the skin with a solution of novocain, and two years later Weiss and Davis,[19] working independently, showed that this acted very efficiently. Since then we have used the method in over 50 cases and our results fully confirm the fact that such pain and tenderness can usually be relieved by local anesthesia. We, like Weiss and Davis, usually used a 2 per cent solution of the drug.

And not only is the referred suffering relieved, but frequently what seems like true visceral pain may also be lessened. Case I is a good example of this. It is an interesting fact that referred pain is more easily got rid of than is true visceral pain. Several observers have noted that a whiff of chloroform may cause it to disappear while the original pain remains as before.

The following are a few examples from our series of cases. They are necessarily very briefly recorded, but it may be said that all

clinical methods were employed in the diagnosis, which in several instances was confirmed by operation.

Selection from Case Epitomes. CASE I.—Male, aged forty-five years. Diagnosis: Aneurysm of the arch of the aorta; syphilis. For the past six months suffered from pain in right chest. Would generally get some relief by local pressure or raising arm above head. Four months ago had to stop work on account of pain and since then has been confined to bed.

January 15, 1929. Is on Gatch frame and any movement in the bed causes pain. There is constant pain also over the third rib anteriorly about 3 inches from sternum.

Observation (a):

11.05 A.M. An area 3.5 by 3 cm. over painful region injected with 12 cc. of 2 per cent novocain intracutaneously.

11.10. The skin is anesthetic to touch.

11.15. Pain is distinctly less and area is not now tender to touch.

11.30. The dull aching in chest is lessening and moving about does not now aggravate it.

11.40. Pain is entirely gone. Patient can now move about without any discomfort.

11.55. Condition unchanged.

12.05 P.M. Pain is still absent.

1.10. Sensation is returning to skin. Pain still absent.

1.30. Pain is returning.

1.40. Pain is back as bad as ever.

Observation (b):

January 26, 1929. The same patient, complaining as before of pain made worse by any exertion. The pain is now chiefly along border of right scapula and there is some ache in right arm.

4.20 P.M. An area 3 by 1½ cm. along right border of scapula was infiltrated with 5 cc. of 2 per cent novocain.

4.25. The dull deep pain is subsiding.

4.27. Moving about or pressing back against chair does not cause pain as formerly.

4.35. Pain all gone from back. Still ache in right elbow.

4.50. Condition unchanged.

5.00. *In statu quo.*

5.20. No pain anywhere and is walking about comfortably.

5.30. Sensation of touch is returning. No pain.

5.55. Pain is returning.

6.30 Pain has returned in old situation beside border of scapula and deep in chest and is worse than before the injection.

NOTE.—Increase in severity of pain doubtless due to his increased activity while under the protection of novocain.

CASE II.—Female, aged fifty years. Diagnosis: Angina pectoris. Frequent attacks of severe pain in chest to right of sternum at the level of fourth rib. Also a tight feeling in upper chest that makes breathing difficult at times

Observation. October 20, 1929: The area of pain is very localized and is tender to touch.

8.30 P.M An area 1 by 1½ inches was injected with 10 cc. of 1 per cent novocain.

8.40. Skin anesthetic to touch; pain is definitely less. Other sensations unchanged.

8.45. The acute pain is gone. There is still some soreness on deep pressure.

8.50. Patient completely relieved.

NOTE.—This patient stated that the relief was more speedy and more complete than with morphia.

CASE III—Male, aged seventy-five years. Diagnosis: Chronic myocarditis and arteriosclerosis. For the last two weeks has had a pain at the angle of the left scapula of a dull aching character.

Observation. March 6, 1929:

2.30 P.M. An area 3.5 by 4 cm. was injected with 10 cc. of 2 per cent novocain.

2.40. Pain has gone and also tenderness.

2.50. Quite free from pain.

3.00. No change.

3.20. Resting quietly.

4.00. Resting quietly. Skin still anesthetic.

4.30. Sensation in skin returning.

5.00. Slight return of pain.

6.00. Pain has returned but not so bad as before.

NOTE.—Next day the pain was as bad as ever.

CASE IV.—Female, aged forty years. Diagnosis: Chronic heart disease and angina pectoris. Symptoms came on during pregnancy four years ago and cardiac reserve gradually lessened, and for last three months much dyspnœa and cyanosis, with cough and some blood-streaked sputum, and much pain.

Observation. February 17, 1929:

9 P.M. Complaining of much pain to left of sternum which is well localized. An area the size of a fifty-cent piece injected with 10 cc. of 2 per cent novocain. In a few minutes complete relief, and patient rested comfortably until 3 A.M.

NOTE.—Patient had often had morphia for her distress and stated that the novocain acted better and more quickly.

CASE V.—Female, aged thirty-eight years. Diagnosis: Cholecystitis. Has been troubled for the last month with flatulence and for the last twenty-four hours with severe pain in the region of the gall bladder which radiates around to the angle of the scapula. It is made worse by pressure and deep inspiration.

Observation. March 1, 1929:

11.55 A.M. An area of 9 sq. cm. over the gall bladder was injected with 20 cc. of 2 per cent novocain.

12.20 P.M. Pain is less over the gall bladder but is worse near the angle of the scapula.

12.25. Six square centimeters at angle of scapula were infiltrated with 16 cc. of 2 per cent novocain.

12.35. All pain gone.

12.50. Pain still absent.

1.00. No return of pain.

CASE VI.—Male, aged forty-seven years. Cholecystitis and duodenal ulcer. Was well until a week ago when he woke nauseated and dizzy, but did not vomit. Much pain in epigastrium, relieved by fluids until yesterday, when the pain became colicky and stabbing. Roentgen ray shows duodenal ulcer but no definite condition in gall bladder.

Observation. January 29, 1929:

5.15 P.M Very severe pain over gall bladder which is aggravated by moving about and is tender to pressure. An area 4 by 3 cm. injected with 10 cc. of 2 per cent novocain.

5.20. The area is anesthetic to touch and the pain is beginning to fade away.
5.25. Pain is entirely gone and also the tenderness over gall bladder. Still same tenderness in epigastrium. Moving or sitting up does not now distress him. Before he could hardly bear being turned over.
5.30. Condition the same. When he moves quickly he gets a twinge of pain in right shoulder.
6.00. Sleeping.
NOTE.—Pain did not return when sensation did. Had a good night.

CASE VII.—Female, aged twenty-six years. Diagnosis: Cholecystitis. Patient took ill twenty-four hours ago when she was seized with severe pain in right upper abdomen and vomited. Diagnosis confirmed by Roentgen ray. Patient refused operation.
Observation. September 7, 1929: Pain is severe over gall bladder region. It is worse on moving and radiates through to the back.
3.40 P.M. An area of 1½ by 1 inches infiltrated with 12 cc. of 2 per cent novocain.
3.50. Some relief. Pain not so sharp.
4.00. Pain has disappeared. Moving about still elicits some pain.
4.15. Quite comfortable.
5.00. Resting.
6.15. Pain is returning.

CASE VIII.—Female, aged twenty-one years. Diagnosis: Subacute appendicitis. Has had continuous pain and tenderness in right lower quadrant of abdomen for the last four days. The pain is aggravated by movement and by deep breathing.
Observation. February 20, 1929:
4.15 P.M. An area 3 by 2.5 cm. was marked off as the point of maximum pain and tenderness and 15 cc. of 2 per cent novocain was injected intradermically.
4.20. Pain is less severe.
4.30. Pain is gone. She can now move and take a deep breath without discomfort.
4.45. Pain is still away. Feels much relieved. Deep palpation elicits slight tenderness, but it requires more pressure than before.
5.00. Condition unchanged.
6.00. No pain over area injected. Slight pain over a new area lower down.
7.00. No pain. Still tender on deep palpation.
7.30. The same.
February 21. Pain returned in the early morning, but not so severe.
NOTE.—At operation the next day appendix found enlarged and club-shaped. Pathologic report was "acute appendicitis."

CASE IX.—Female, aged thirty-five years. Diagnosis: Carcinoma of the stomach, confirmed by Roentgen ray. For the past year or more has had pain in epigastrium with nausea and occasional vomiting. Pain radiates through to the back, and at the time of the treatment was in the left back just under the angle of the scapula.
Observation. August 21, 1929:
2.50 P.M. The painful spot, about 1 inch square, was infiltrated with 6 cc. of 2 per cent novocain.
2.55. Pain is less and hard to localize.
3.00. Pain has shifted to an area directly below the one injected.
3.05. The second area injected.

3.10. Pain has entirely gone.
3.20. Condition comfortable. No pain.
3.40. No change.
3.55. No change.
4.50. Pain is returning.

CASE X.—Female, aged twenty years. Diagnosis: Acute salpingitis. Has had profuse purulent vaginal discharge for over a year with pain in lower abdomen which is acute during menses, especially the last two. The pain is now localized to an area 2 by 2 inches above Poupart's ligament on the right side.

Observation. July 12, 1929:

12.15 P.M. Sixteen cubic centimeters of 2 per cent novocain used intracutaneously.
12.20. Area is anesthetic to touch and pain is less.
12.50. Pain now gone. Can move about comfortably. Deep pressure elicits some pain.
1.20. No pain. Sensation is absent.
2.00. Condition the same. Sensation to touch is returning. Patient vomited and had cold sweat.
2.20. Has occasional twinges of pain, but only slight.
3.30. No return of pain. Sensation completely returned.
8.00. Pain has returned with original severity.

July 13:

2.00. Pain in old area and 15 cc. of 2 per cent novocain injected.
3.00. Pain left her in ten minutes but tender on deep pressure.

NOTE.—The pain was similarly relieved on three succeeding days.

CASE XI.—Male, aged thirty-three years. Diagnosis: Spasm of the sigmoid flexure of the colon. For the last six months or so patient suffered from flatulence and occasional vomiting, with severe cramps in abdomen. At first had some diarrhœa without blood or mucus, but lately constipated and bowels moved only with enemata. Roentgen ray shows nothing except severe spasm of the sigmoid flexure which synchronizes with the paroxysms of pain.

Observation. The pain occurs rather indefinitely about the umbilicus and at times spreads around to back.

February 6, 1930:

4.30 P.M. Although the pain was hard to localize, it was more or less about the umbilicus, and an area 4.5 by 3 cm. on right side midway between the umbilicus and Poupart's ligament was infiltrated with 9 cc. of 2 per cent novocain.
4.35. Anesthesia, but no change in pain.
4.40. No change.
4.50. No change.
5.00. No change.
5.30. No change.
7.00 Sensation in skin has returned.

NOTE.—Possibly if a very large area had been infiltrated some relief might have resulted, but none came from what was done.

CASE XII.—Male, aged thirty-five years. Diagnosis: Ureteral colic. Was taken suddenly ill on December 15 with acute pain in the left flank. This came on while he was walking home from work and he only reached his house with difficulty. Laxatives and enemata were used without effect. There was some pain on passing water and the urine showed some pus and red blood cells, and the benzidin test for blood was positive. No stone was visible in a flat Roentgen ray plate.

Observation. December 16, 1929: Severe pain in left flank just below the ribs.

3.55 P.M. An area 1½ by 2 inches at site of pain was injected with 10 cc. of 2 per cent novocain.

4.00. Skin anesthetic to touch and pain is less severe.

4.10. Patient is resting quietly and is quite comfortable.

4.20. Pain is quite gone. There is tenderness on deep pressure lateral to the injected area. A second injection of 2 cc. relieved this considerably.

4.30. Patient is free from pain and is resting comfortably.

NOTE.—The pain did not return. Probably the novocain reflexly relieved the spasm of the ureter.

CASE XIII.—A healthy male volunteer swallowed a toy balloon attached to a rubber tube and pressure gauge. Under the Roentgen ray screen the barium-treated balloon could be seen lying in the lower part of the esophagus. The pressure in the esophagus varied from 20 to 240 mm. of mercury, the latter during a spasm of vomiting.

After a period of rest the pressure in the balloon was slowly raised to 40 mm. Hg. and the subject felt definite pain over the lower part of the sternum. This area was quickly infiltrated with 5 cc. of 2 per cent novocain and soon the pain shifted lower down. The second area was injected and then the pain was in the epigastrium. This area was infiltrated and for two minutes there was no pain and then it appeared over the upper part of the sternum. A fourth injection was given and after this any increase in the pressure in the balloon caused no surface pain but a peculiar deep discomfort which could not be localized. There was no pain in the back at any time in the experiment.

NOTE.—This experiment was repeated on several volunteers with practically the same results.

The injections were done with a thin flexible needle intracutaneously so as to produce raised white wheals. Subcutaneous injection did not produce anesthesia, nor did relief occur if the injection was away from the painful area, showing that the results were not due to any systemic effect. Intracutaneous injection with normal saline produced some anesthesia and relief of pain, but the effects were only partial and very transient.

In many of the cases the pain was completely relieved by the injection; in some the superficial pain was lessened but a deep sense of discomfort remained; in several both superficial and deep pain disappeared. Where no definite superficial pain was present, but only deep suffering, as in intestinal colic, no relief was obtained by injecting over the surface. The very large area covered by such applications as fomentations and poultices may explain why these act.

In many instances the superficial pain was relieved but at once appeared lower down or to one side as was well shown in Case XIII. This condition, called *allocheiria*, is explained by the excitation spreading to adjacent centers in the central nervous system.

Discussion. These cases show that it is usually easy to relieve the referred part of visceral pain by local anesthesia, and also sometimes to dull to some extent what appears to be true visceral pain. While this fact is so evident most writers on the subject of referred

pain do not discuss its bearing on the nature of the phenomenon. Mackenzie, Head and Hurst do not mention it. Morley,[2] while giving many beautiful examples of the relief of the pain by local anesthesia, confines himself to the thesis that the pain is a peritoneo-cutaneous reflex phenomenon.

There have been however, several theories advanced as to how local anesthesia acts. Verger[20] suggests that the effect is due to an action on the theoretical connections in the skin between the cerebrospinal and sympathetic nerve endings. Sicard and Lightwitz[21] believe that what they call "cutaneous shock" occurs, this shock sending up an inhibitory impulse which breaks the synapses between the sympathetic and cerebrospinal cells in the posterior root ganglia and especially in the cord. They put all forms of cutaneous therapy under the same heading and the action they believe is one of counterirritation. According to them intradermic infiltration with any nonacid solution acts as well as does novocain. As they put it, "intradermic injections appear in fact the modern method of using cutaneous therapy formerly so much employed in the form of cauteries, setons and blisters." Such counterirritation may account for some cases, but certainly in our experience normal saline injections do not relieve the pain nearly as well as does novocain and also it is hard to look upon gentle warmth as a form of counterirritation.

Lemaire[18] insists that the novocain or other chemical anesthetic relieves pain by directly spreading up the nerves to the root ganglia as do the toxins of rabies and tetanus. Such a theory is hard to follow and certainly heat and cold cannot act in this way and yet often soothe pain efficiently. Weiss and Davis[19] believe that the relief is due to the checking of the normal afferent impulses from the surface that are now, by reaching exciting centers, felt as pain, and hold that this supports Mackenzie's theory of referred pain. This theory of all pain in visceral disease was that the unfelt afferent impulses from the damaged viscus on reaching the cord spread to and excite neighboring cells including those of the cerebrospinal system. Normal afferent impulses now arriving from the surface are hence felt as pain.

While not for a moment agreeing that all pain from a viscus is felt in the parietes, our results suggest that an intact reflex arc, including the somatic portion, is essential for the appreciation of referred pain. The somatic neurons appear to require to be in a state of what might be called sensory tone or tension before they will respond to the afferent impulses coming from the irritated viscus or, indeed, from anywhere. A violin string will not vibrate in response to the irritation of the bow unless it be sufficiently tense and in an analogous way the cerebrospinal neuron must be in a state of tenseness or tone before referred pain occurs. Whether or not this tenseness is dependent upon the normal afferent impulses

from the periphery or upon some other fact or certain it is that numbing the terminations of the nerves stops the referred response to impulses coming from the region of the viscus. The somatic neuron is no longer intact.

Further, Weiss and Davis[19] noted that "different types of sensation (pressure, heartburn, choking sensation, etc.) 'felt inside' were relieved by the infiltration of the skin," and everyone knows how such deep sensations are eased by soothing surface applications. They argue from this that these deep sensations are really referred to the parietes, but this, in our opinion, does not at all follow. We also noted that often deep discomfort was lessened by surface anesthesia but may not this be because the stopping of the parietal afferent impulses lessens the excitability of the visceral neurons, which now, having less tenseness, do not so easily respond to the messages coming from the irritated viscus? In the same way may be explained why surface numbing lessens various visceral reflexes and so eases colic and possibly visceral congestion. Adrian and Zotterman[23] have shown that the ascending impulses in a sensory nerve may vary from 7 to 100 per second, depending upon the intensity of the stimuli, and in proportion as these are lessened by surface anesthesia so will be the excitability of the centers. On the other hand, increasing the afferent impulses from the surface often increases deep pain, as seen when sudden chilling intensifies the pain of angina and may induce colic.

Lastly it is evident that in referred pain the suffering may be lessened by an attack on either end of the viscero-sensory reflex arc. Thus, the referred pain in angina pectoris can be diminished by anesthetizing the painful area on the surface or more specifically by relieving the tension in the heart or aorta by lowering the blood pressure; the surface pain in biliary colic may be wiped out by infiltrating the skin or by relaxing the biliary passages by benzyl benzoate; that of duodenal ulcer by anesthetizing the skin or by the administration of alkalies, and so on.

Conclusions. 1. True visceral pain exists. It is usually dull but may be very acute.

2. Such visceral pain may occur alone or be accompanied by referred pain which will appear in the distribution of the somatic nerves that come from the segment of the central nervous system with which the affected visceral nerves are connected.

3. In many instances the referred pain is the only one that reaches the level of consciousness.

4. Referred pain is more easily relieved than is that coming from the source of the irritation. This relief can be obtained by the use of various anodyne applications and especially by the infiltration of the skin by anesthetics, such as novocain.

5. Often such anodynes will also, to a certain extent, relieve the deep suffering, but sometimes this is not the case and the afferent

impulses from the source of irritation may, without any amplification from the periphery, be sufficient to reach the sensorium.

6. When a referred pain is present it may be relieved either by attacking it at its distribution or, more specifically, by directly treating the cause of the irritation.

7. The theory advanced here is that for referred pain to occur it is essential that the whole sensory reflex arc be intact.

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REVIEWS.

AFFECTIONS OF THE EYE IN GENERAL PRACTICE. By R. LINDSAY REA, B.Sc., M.D., M.Ch., F.R.C.S. Pp. 155; 40 illustrations. Philadelphia: Lea & Febiger, 1930. Price, $3.50.

THIS small book is written primarily to assist the general practitioner in the diagnosis and treatment of the more common diseases of the eye. The author expresses himself in a clear and concise manner, and covers the ground adequately. He also stresses certain cases that should be referred to the specialist. There are sixteen chapters in the book. The first seven deal with the diseases of the various anatomical structures of the eye, beginning with the lids and working backward. There are also chapters on glaucoma, errors of refraction, squint, injuries to the eye, cataract, the examination of the eye in diseases of the nervous system, localizing value of eye symptoms in the diagnosis of diseases of the brain, the orbit, and the hygiene of the eyes. A list of therapeutic formulæ and an adequate index conclude the volume.

The author is to be congratulated on covering the ground in such a concise and practical manner. This book would be an asset to any general practitioner's library. A. F.

ANNALS OF ROENTGENOLOGY, VOL. XI. THE CHEST. By L. R. SANTE, M.D., F.A.C.P., F.A.C.R., Edited by JAMES T. CASE, M.D. Pp. 561; 246 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, $20.00.

THE author has admirably accomplished his purpose as stated in the preface, namely, that this volume was undertaken "for the aid of the clinician and to serve as a compilation for the guidance of roentgenologists." He has attempted to lay down the broad general principles of roentgenology of the chest, avoiding detailed discussion of individual subjects. The volume is, therefore, a distinct addition to reference works on roentgenology. It will serve as a firm foundation for the beginner and as an excellent guide to the experienced roentgenologist.

The plan of presentation of the subject is very good. Due consideration is given to the technique of roentgenologic examinations, the Roentgen anatomy of the chest, the physiology of respiration and the principles of roentgenologic interpretation. Of special merit is that portion of the book devoted to roentgenologic evidences of disease. Here numerous diagrams are used to illustrate the various types of pathologic processes to be encountered in the lungs. The major portion of the volume is devoted to the roentgenologic characteristics of individual diseases. The work is profusely illustrated by diagrams and reproductions of roentgenograms. These are accompanied by rather full and concisely stated explanatory notes.

While this book will be primarily of interest to roentgenologists, there is much that the clinician will find of interest and value in its contents. K. K.

CLIO MEDICA, VOL. I. THE BEGINNINGS—EGYPT AND ASSYRIA. By WARREN R. DAWSON, F.R.S.E. Pp. 86. New York: Paul B. Hoeber, Inc., 1930. Price, $1.50.

THIS interesting book auspiciously inaugurates "Clio Medica," a series of conveniently small, inexpensive but invaluable volumes that present in a concise and pleasantly readable form certain aspects of the long, complex but fascinating history of the origin and development of the medical sciences. The author of this first volume of the series is a distinguished authority in all matters of ancient medical lore.

His contributions concerning medical history, many and valuable, are, fortunately, based upon direct and prolonged study of the earliest medical inscriptions, papyri and manuscripts and not upon opinions derived from reading.

It has been well and truly said that a science or an art is best understood when its origins are known.

The author turns back the pages of time to the very beginnings of written medical history in an authoritative but pleasing style and makes the reader aware of the exact truth of Charcot's statement that "disease is of old and nothing about it has changed. It is we who change as we learn to recognize what was formerly imperceptible."

The book is an excellent antidote for egoism and complacency, traits inexcusable in a member of the medical profession, for it clearly reveals that our advance in knowledge and vision is a result of our being able "to stand upon the shoulders of those of our profession who paved the way for us." If all the volumes of "Clio Medica" prove as instructive and thought-productive as "The Beginnings" the entire medical profession will owe a debt of gratitude to the Editor. E. B.

ENDOCRINE DISORDERS. By PROF. HANS CURSCHMANN. Pp. 188; 46 illustrations. London: Oxford University Press, 1929. Price, $4.00.

IN a field where so much has been claimed on too little evidence, it is a pleasure to read this conservative, evenly balanced little book. It is well written, concise but adequate, and should be of particular value to the practitioner and the medical student. Illustrations are numerous and well chosen. Quite up to date at the time of publication, yet it dismissed with a paragraph, as "purely speculative," human hyperparathyroidism, established within a few months as a clinical entity. R. K.

THE COMMON HEAD COLD AND ITS COMPLICATIONS. By WALTER A. WELLS, A.M., M.D., F.A.C.S. Pp. 225; 15 illustrations. New York: The Macmillan Company, 1929. Price, $2.75.

THE author states as the object of this book the presentation to the layman of "the best and most recent knowledge of the profession on the subject of the origin and nature of the common cold and its complications—why we catch them, how we can avoid them and what we can do to get rid of them." This he has succeeded in doing very well and the reader will find the work adequate, well expressed, interesting and accurate. The Reviewer is, however, a bit puzzled over what purpose might be served in a book for laymen by an illustration of the author's method of vessel ligation in tonsillectomy. R. K.

OUTLINE OF PREVENTIVE MEDICINE. By twenty-one contributors. Pp. 398. New York: Paul B. Hoeber, Inc., 1929. Price, $5.00.

MOST works on preventive medicine have presented the subject from the standpoint of the specialist in public health, hygiene and sanitation. This book, on the contrary, is written expressly for medical practitioners and students, with the purpose of emphasizing preventive measures as applicable in general practice. A group of eminently qualified writers have contributed chapters on such subjects as the Periodic Health Examination; General Medicine; the Surgical Aspects; preventive medicine in the specialties: Allergy, Tuberculosis, Orthopedics, Obstetrics, Gynecology, Pediatrics, Nervous and Mental Disease, Dermatology, Urology, Venereal Diseases, Diseases of the Eye, Ear, Nose and Throat, Industrial and Occupational Diseases, etc. The various fields have been adequately and well presented. The chapters on the general medical and the surgical aspects are, however, too short, with more emphasis on early

diagnosis than on original prophylaxis. There is some unnecessary duplication (for example, asthma, tetanus, diphtheria, syphilis, rabies, etc.). Three pages are devoted to typhoid fever, but only three lines to undulant fever of bovine origin. These are, however, minor defects; the book really represents a valuable contribution to this important field and is to be recommended highly to practitioners and students. The volume itself is a very creditable product of the bookmaker's art. R. K.

DISEASE AND THE MAN. By GEORGE DRAPER, M.D. Pp. 270; 52 illustrations. New York: The Macmillan Company, 1930. Price, $4.50.

IN this volume are set forth the author's further studies since the publication in 1924 of his book, *Human Constitution*. The argument: If persons with certain disease tendencies are subjected to analysis of their morphology, physiology, psychology and immunology, there is found a high degree of correlation between these phases of the individual, so that knowledge of one phase makes it possible to predicate, at times with surprising accuracy, the characters constituting one or more of the others. The part played by heredity, modified by environmental factors, in determining the individual's constitution is discussed in the chapter on Genetics. Under Morphology are described methods of anthropometry and findings in a number of disease groups. There follow chapters on The Influence of Sex, on The Psychologic Panel, a Clinic for the Presentation of Constitutional Type (as given by the author before senior medical students) and a closing chapter: The Patient and His Physician (originally written as a lecture for laymen, even more valuable to physicians). The whole subject is most important and as the author, a pioneer in the field, presents it, one of great interest and fascination. Physicians and medical students will find this book instructive and delightful reading. R. K.

WHAT EVERYONE OUGHT TO KNOW. By OLIVER T. OSBORNE, M.D. Pp. 313. Springfield, Ill.: Charles C. Thomas, 1929. Price, $2.50.

APPLIED physiology and hygiene for popular consumption. The author's book contains a surprising amount of information; the advice is sane, sound and is wholly untainted with the "fad" tendencies so common among those who undertake to tell us how to regulate our lives and bodies. In fact, the Reviewer would find nothing with which violently to disagree (he was delighted with the chapters on Nutrition, Foods, Diet and Promotion of Health; a bit

surprised at the alleged villainous character of the bristle tooth brush and at the omission of the alcohol question; he is sure that the statement, "It is the iron constituent of the blood that changes the carbon dioxide to oxygen" was unintentional). The style is chatty, occasionally a bit garrulous and tautologic, but always interesting. Physicians may well recommend this excellent book to their families and patients. R. K.

REPORT ON MUSSEL PURIFICATION. By R. W. DODGSON, M.D. (LOND.), M.R.C.P. (LOND.), M.R.C.S. (ENG.). Pp. 498; 65 illustrations. London: His Majesty's Stationery Office, 1928. Price, £1, 1s.

THIS exhaustive study deals primarily with the subject of mussels, but much of the data is applicable also to shellfish in general and to oysters in particular.

The principal topics considered are: pathologic conditions which may follow the consumption of mussels (typhoid, mussel poisoning and the like); the pollution of shellfish beds, together with methods of detection, prevention and palliation; the physiology of mussels and experimental and practical methods of purifying them when polluted; tests to determine the efficiency of purification; bacteriologic methods and standards of purity.

The book is well printed on a good grade of paper, and is serviceably bound. The illustrations are excellently done and instructive. There are 126 bibliographic references.

The principal use for this work will be in the hands of public health workers and those concerned with the cultivation of shellfish. F. L.

THE BACTERIOPHAGE AND ITS CLINICAL APPLICATIONS. By F. D'HERELLE, Professor of Bacteriology. Pp. 254. Springfield, Ill.: Charles C. Thomas, 1930. Price, $4.00.

THIS book is well printed, on a good quality of paper, and is serviceably bound.

The subject matter is divided into seven chapters, dealing respectively with Bacteriophagy, Bacterial Mutations, Nature of Bacteriophage, Infectious Disease, Recovery and Immunity, The Use of Bacteriophage, and Conclusions.

These sections cover the essentials necessary to an understanding of the development and mechanism of bacteriophagy.

The material is logically and interestingly presented, in a style which can be readily followed, although the author states his views with such finality that one cannot help feeling he attaches too little

weight to conclusions of other workers who also have contributed to our knowledge of this important subject.

Since this book is intended primarily for physicians, there is too little space devoted to the methods of preparation of bacteriophage filtrates and the details of their therapeutic use. It seems to the Reviewer that it would be well if there were more discussion of the type of cases in which bacteriophage therapy is unsuccessful, and, if possible, the reasons for the failures reported by other observers, and suggestions for overcoming them. F. L.

INCOMPATIBILITY IN PRESCRIPTIONS AND HOW TO AVOID IT. By THOMAS STEPHENSON, D.Sc., PH.C., F.R.S. (EDIN.), F.C.S. Pp. 61. New York: Paul B. Hoeber, Inc., 1929. Price, $1.50.

A CONCISE statement of the general principles underlying incompatibilities, following an outline form, with numerous examples and a list of incompatibilities according to drugs, alphabetically arranged. A valuable book, it would have been made still more so if it had been made up in a handy pocket size. R. K.

ALIMENTARY ANAPHYLAXIS. By GUY LAROCHE, CHARLES RICHET FILS and FRANCOIS SAINT-GIRONS, Paris, France. Forward by PROF. CHARLES RICHET of the Faculty of Medicine of Paris; translated by MILDRED P. ROWE and ALBERT H. ROWE, M.D. Preface by ALBERT H. ROWE, M.D. Pp. 139. Berkeley: University of California Press, 1930. Price, $2.00.

WRITTEN in 1919 by three French physicians who theorized rather far on the basis of their clinical observations, this little book on food allergy has found much confirmation in the intervening years. It will be of interest to those engaged in this special field. The translation is excellent. R. K.

BOOKS RECEIVED.

NEW BOOKS.

The Surgical Clinics of North America, Vol. 10, No. 4 (Southern Number, August, 1930). Pp. 268; 96 illustrations. Philadelphia: W. B. Saunders Company, 1930.

Medical and Surgical Year Book, Physicians Hospital of Plattsburgh, Vol. 1, 1929. Pp. 322; illustrated. Plattsburgh: The William H. Miner Foundation, 1930.

* Reviews of titles followed by an asterisk will appear in a later number.

*Dietetics and Nutrition.** By MAUDE A. PERRY, B.S. Pp. 332. St. Louis: The C. V. Mosby Company, 1930. Price, $2.50.

*Krankheiten und Hygiene der Warmen Länder.** By PROF. DR. REINHOLD RUGE, PROF. DR. MÜHLENS, and PROF. DR. MAX ZUR VERTH. Pp. 494; 496 illustrations. Verlag, Leipzig: Georg Thieme, 1930. Price, M. 39.60.

Heat Pyrexia. No Heat Stroke. No Heat Fever. By C. J. MCCARTIE: M.A., M.D., M.CH., LT-COL., I. M. S. (retired). Pp. 27. Dublin, Browne & Nolan, 1930. Price, 1/–.

*Recent Advances in Chemotherapy.** By G. M. FINDLAY, O.B.E., M.D., D.Sc., with a Foreword by C. M. WENYON, C.M.G., C.B.E., M.B., B.S., B.Sc., F.R.S. Pp. 532; 15 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1930. Price, $3.50.

*The Physiology of the Vestibular Apparatus.** By MARIO CAMIS; translated and annotated by R. S. CREED, B.M., B.CH., M.A. Pp. 310; 65 illustrations. New York: Oxford University Press, 1930. Price, $7.50.

*Tropical Medicine in the United States.** By ALFRED C. REED, M.D. Pp. 410; 60 illustrations. Philadelphia: J. B. Lippincott Company, 1930. Price, $6.00.

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*Handbook of the Vaccine Treatment of Chronic Rheumatic Diseases.** By H. WARREN CROWE, D.M., B.CH. (OXON.), M.R.C.S., L.R.C.P. Pp. 52. New York: Oxford University Press, 1930. Price, 80¢.

*Elements of Psychology for Nurses.** By REV. JAMES FRANCIS BARRETT. Pp. 326; 8 illustrations. Milwaukee: The Bruce Publishing Company, 1930. Price, $2.50.

*Feeding in Infancy and Childhood.** By I. NEWTON KUGELMASS, M.D., PH.D., Sc.D. Pp. 345; 37 illustrations. Philadelphia: J. B. Lippincott Company, 1930. Price, $6.00.

*Burns—Types, Pathology and Management.** By GEORGE T. PACK, B.S. M.D., and A. HOBSON DAVIS, B.S., M.D. Pp. 364; 60 illustrations. Philadelphia: J. B. Lippincott Company, 1930. Price, $6.00.

*Chronic Nasal Sinusitis.** By PATRICK WATSON-WILLIAMS. Pp. 221; 110 illustrations. New York: William Wood & Co., 1930. Price, $5.00.

NEW EDITIONS.

*Injuries to Joints.** By SIR ROBERT JONES, BART., K.B.E., C.B. Pp. 195; 29 illustrations. Third edition. New York: Oxford University Press, 1930. Price, $2.00.

*Manual of Physiology.** By H. WILLOUGHBY LYLE, M.D., B.S. (LOND.), F.R.C.S. (ENG.), and DAVID DE SOUZA, M.D., D.Sc. (LOND.), F.R.C.P. (LOND.). Pp. 820; 138 illustrations. Third edition. New York: Oxford University Press, 1930. Price, $5.25.

*A System of Clinical Medicine.** By THOMAS DIXON SAVILL, M.C. (LOND.). Pp. 1019; 167 illustrations. Eighth edition. New York: William Wood & Co., 1930. Price, $10.00.

*Personal and Community Health.** By CLAIR ELSMERE TURNER, M.A., DR. P.H. Pp. 443; 62 illustrations. Third edition. St. Louis: The C. V. Mosby Company, 1930.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Immunity of Certain Anatomic Regions From Lesions of Skin Leprosy.—Leprosy is by no means an easy disease to diagnose. Under certain conditions the typical case may be recognized by the tyro. On the other hand, men with extensive experience with the disease are often at a loss to know if the patient does not or does have the disease. HOPKINS, DENNEY and JOHANSEN (*Arch. Dermat. and Syph.*, 1929, **20**, 767) have studied the location of the lesions of leprosy in 302 patients, 245 of whom had typical leprous skin lesions. They write that certain areas of the body are conspicuous as a result of their exemption from the involvement of the leprous lesion. This is certainly a diagnostic observation of considerable importance. The areas in which macules, infiltrated patches and nodules of leprosy practically never occurred are those sites which are least exposed to irritation from such sources as sunlight, heat, cold, pressure, friction and other stimuli likely to produce local hyperemia. The posterior inferior auricular area, the cavum conchæ, the orbital surface of the nose, the lateral palpebral area, the axilla, the inframammary fold in women, the interdigital surface and the perineum were exempt from lesions in all cases. The scalp, mesolabial fold and the sulcus of the upper eyelid were involved in only 2, 4 and 2 instances. The authors suggest that in these areas mentioned conditions are not favorable to the growth of the bacillus of Hansen.

Recoveries from Leprosy.—AN ANALYSIS OF THE RECORDS OF 65 CASES.—DENNEY, HOPKINS and JOHANSEN (*Pub. Health Rep.*, 1930, **45**, 667) report on 65 patients who have been admitted to the National Leper Home at Carville with leprosy and who have been discharged from that institution as cured. They make a note in their paper that between the time of the presentation of this report and January 23,

1930, 8 additional lepers were paroled. This makes a total series of 73 patients who have been observed in the last ten years in whom there have been something under 3 per cent of relapses. This is a very remarkable record, indeed, and it discounts clearly the idea held from time immemorial that leprosy is incurable. Some of these patients had been in the leprasorium for many years. Some of them had no sequelæ of leprosy when they were discharged and few of them had marked leprous sequelæ, such as total blindness, loss of all phalanges and similar leprous lesions. The majority of these patients received chaulmoogra oil; 55 received a crude oil; 12 received intramuscular injections of benzocain-chaulmoogra oil; 21 received ethyl esters of chaulmoogra oil by intramuscular injection. It should be appreciated that in this group of patients many received several forms of treatment. In addition to those who may have received chaulmoogra oil by mouth as well as by injections, there are some who were given mercurochrome intravenously, several who took Fowler's solution and several who were given salvarsan. In addition to the chaulmoogra oil and more or less specific treatment, certain hygienic, physiotherapeutic and psychotherapeutic measures were also employed in the treatment of these patients. Of these 65 patients whose clinical history is detailed in the report, 12 were of the nodular type of leprosy, who remained in the hospital on an average of five and four-fifth years. Twenty-six of the patients were of the mixed type, hospitalized for an average of five and a half years, and 27 of the paroled cases were of the anesthetic type with an average period of hospitalization of nine years. This splendid record of cures must be of tremendous interest to the leper himself. One of the features of the disease that has to be combated most consistently is the tremendous mental depression under which the patients labor. Knowledge of the increased tendency to cure the disease should certainly greatly enhance the possibility of ultimate recovery.

The Circulatory Failure of Diphtheria. III. The Treatment of the Circulatory Failure of Diphtheria.—In an earlier communication SCHWENTKER and NOEL discussed the evidence which indicated to them that circulatory failures in diphtheria may be of two types: an early failure occurring as a part of a general toxemia, and late failure probably due to inflammatory reactions in the heart and conduction system developing during the process of regeneration and repair. They (Schwentker and Noel, *Bull. Johns Hopkins Hosp.*, 1930, **46**, 359) now write that: as the mechanism of production of the two types of circulatory failure differ so essentially, it correspondingly follows that the treatment of the two types of failure should be entirely different. In the acute, early failures because of the disturbance of carbohydrate metabolism that occurs in diphtheria poisoning, glucose should be given in large quantities at frequent intervals and guarded by insulin. Specifically, the general management of such cases includes a preliminary dose of antitoxin, mentioned in the article as being "large." If no reaction has taken place a half an hour later, 10,000 to 20,000 units of antitoxin plus 20 gm. of a 50 per cent solution of dextrose are given,

10 to 20 units of insulin being given with the dextrose. At intervals from ten to twenty-four hours, the intravenous injection of dextrose is repeated, always being supplemented by insulin, a unit of insulin for each 1 to 2 gm. of dextrose. After the first two injections a 10 per cent solution of dextrose is given in order to get the beneficial effects of the additional fluid. In the 14 patients that they treated in this manner, all of whom appeared close to death, several of whom were unconscious when first seen, 13 survived.

Experimental Epidemiology of Tuberculosis. The Effect of Crowding Upon Tuberculosis in Guinea Pigs, Acquired by Contact and by Inoculation.—LURIE (*J. Exper. Med.*, 1930, **51**, 729) writes that there has been some question as to whether or not normal guinea pigs in the same room but not in the same cage with tuberculous animals may acquire the disease. In order to reinvestigate the question he exposed 103 guinea pigs who apparently were nontuberculous in the same room with a series of animals that had the disease. Fifteen of these pigs, or 14.5 per cent, developed tuberculosis after a long period of exposure, the shortest time in which tuberculosis developed being eight months. Most of the guinea pigs were exposed for thirty-two months without becoming tuberculous. The possibility arises that this freedom from the disease may be due to a natural resistance to tuberculosis or to an acquired immunity developed after long-continued exposure. The animals that died evinced a characteristic chronic type of the disease. There was marked involvement of the lungs, frequently cavity formation, extensive tuberculosis in the tracheobronchial lymph nodes, while the cervical and mesentery glands were but slightly affected.

SURGERY

UNDER THE CHARGE OF

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Bone-block Operation for Dropfoot: Analysis of End Results.—CAMPBELL (*J. Bone and Joint Surg.*, 1930, **12**, 317) claim that that the object of the method is to construct an osseous process posterior to the ankle joint, which is attached to the os calcis and which will impinge upon the articular surface and the posterior surface of the tibia, blocking ankle motion at about 10 degrees of plantar flexion. The operation is simple, as the bone for transplantation is usually available from associated operative procedures. Apparatus may be discarded as a natural internal brace is constructed. Muscle power is conserved by overcoming the constant force of gravity. Prevention of overstretching may of itself permit a return of dormant muscle power. Rocker

motion of the ankle joint is conserved. Stabilization is rendered more effective by the bone block and incident additional fusion induced between the astragalus and the os calcis. The percentage of satisfactory and permanent end results in the stabilization of paralytic feet has been found to be thus materially increased.

Goitrous Enlargement of the Thyroid Gland Due to Amyloidosis.—HUNTER and SEABROOK (*Arch. Surg.*, 1930, **20**, 762) state that a reported instance of advanced amyloidosis of the thyroid gland, producing enlargement of the gland and symptoms of pressure stenosis of the trachea, is chronic pulmonary tuberculosis. It is the most common cause of amyloid formation and adequately explains its presence in this case. The results of the Congo-red absorption test indicates that the patient did not have a widespread amyloidosis. The present study confirms the observation of previous investigators that in the thyroid gland amyloid substance is deposited chiefly in the vascular interalveolar spaces. Amyloidosis of the thyroid gland is seldom encountered in surgical practice. The nature of the process may be suspected or diagnosed at operation by the bacon-like or fatty appearance of the gland and distinguished from a malignant process by the almost complete lack of hemorrhage during the course of the operation.

Carcinoma of the Small Bowel.—RANKIN and MAYO (*Surg., Gynec. and Obst.*, 1930, **1**, 939) refer to the cases of carcinomata and sarcomata reported in the literature, but base their study on the carcinomata of the small bowel appearing in The Mayo Clinic from and including the year 1919, Judd having reported on the cases before that year. Between January 1, 1919, and October 1, 1929, inclusive, carcinoma occurred in the small bowel 31 times as compared with 2775 times in the large bowel and rectum and 2646 times in the stomach. Adding Judd's cases, reported in 1919, there have been 55 cases of carcinoma of the small intestine compared with 4597 of the large bowel and rectum together, and 4335 of the stomach. It represents, at The Mayo Clinic, 0.062 per cent of the cases of carcinoma of the gastrointestinal tract. The primary signs and symptoms are directly relative to intermittent obstruction and to secondary anemia. Duration of symptoms varies with the individual case, but the average is fourteen to fifteen months. A movable tender mass that "slips away from the fingers" should arouse suspicion. The tendency, as noted in the history, is for constipation to be a rather constant symptom and for it to become increasingly obstinate, although occasionally it is interspersed with attacks of diarrhea. Repeated tests for occult blood are important in suspicious cases. Roentgenologic examination is of particular importance only from a negative standpoint in the present state of knowledge, but it seems likely that future progress along diagnostic lines will make the roentgenologic examination much more accurate and definite. Resection and end-to-end anastomosis is the surgical procedure of choice. When this is not possible lateral enteroanastomosis should be done to short-circuit the obstruction. The prognosis is poor regardless of the procedure. Metastasis takes place early.

THERAPEUTICS

UNDER THE CHARGE OF

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Investigations on the Action of Novasurol on Trichinosis in Rats.—Citing the very favorable results in the treatment of 2 cases of trichinosis in man reported by Jochweds and Pekielis, CHÜKRI (*Klin. Wchnschr.* 1930, **9**, 298) made a series of carefully controlled studies on the action of novasurol on trichinosis in rats, from which he finds that novasurol exerts no inhibitory or destructive action on the intestinal, blood or intramuscular trichina. Furthermore there is no apparent influence on the course of the disease in rats caused by the injection of novasurol.

The Use of Emetin in Nonamebic Abscesses of the Lung.—Evidence is available in the literature that emetin is a useful therapeutic agent in a number of other conditions besides amebiasis. Its use is advocated in certain cases of acute and chronic bronchitis, in spirochetosis of the lungs, and in cases of pulmonary hemorrhage. NUBERT and BRANISTEANU (*Presse méd.*, 1930, **9**, 132) have used emetin hydrochlorid with beneficial effect in 2 cases of nonamebic pulmonary abscesses and in 4 cases of purulent non-"fuso-spirochitic bronchitis." In one of the patients with pulmonary abscess daily subcutaneous injections of 0.04 gm. of emetin hydrochlorid resulted in prompt decrease of the fetid expectoration. In about seventeen days the patient felt well and Roentgen ray examination showed that the shadow due to the abscess had disappeared. In the other cases, repeated injections of doses of 0.02 and 0.04 gm. caused the disappearance of the purulent nature of the expectoration but the objective evidence of the pulmonary pathology persisted. The authors claim that in purulent bronchitis emetin is a useful drug; it causes a decrease in the amount of the secretion and the disappearance of the fetid odor of the sputum. It also causes improvement in the general condition of the patient.

Endonasal Application of Insulin.—WASSERMEYER and SCHAEFER (*Med. Klin.*, 1930, **26**, 474) report the results of investigations designed to determine whether or not a satisfactory method for administering insulin intranasally could be developed. They employed in their tests both normal persons and those suffering from the milder forms of diabetes. To these, under well-controlled conditions, they administered insulin intranasally in the form of powders, as well as in solution, and in doses varying between 10 and 100 units. Control observations were

made with the administration of the same preparation of insulin by the usual subcutaneous method. Among the preparations studied were dried insulin powder mixed with sodium borate, with saponin, caffein, theocin and primary phosphates. They also employed a mixture of insulin with desoxycholic acid. Of these the most effective and the least objectionable was the mixture with sodium borate. That with desoxycholic acid proved irritant and was very objectionable in taste. That with saponin was very irritant, while the remaining mixtures exerted no insulin action. Simple solutions of insulin in water or in physiologic saline were administered in the form of sprays and also by means of cotton tampons saturated with the solution. With these solutions applied by either method and with the powder containing sodium borate they observed in both normal and mildly diabetic persons inconstant and only mild reductions in the blood sugar together with the frequent reappearance of sugar in the urine shortly after the administration. They found further that no greater effects were produced by doses of 50 to 100 units than were obtained in the same persons from doses of 10 to 20 units. Efforts were made to determine the reason for the frequent ineffectiveness of nasal administration and the reason for the failure of large doses to be more effective than small ones, but these efforts yielded no satisfactory explanation. The authors conclude that the endonasal administration of insulin may be of slight value in mild cases of diabetes, but that it is not of sufficient trustworthiness to warrant its recommendation.

The Treatment of Carbon Monoxid Poisoning by Ultraviolet Irradiation.—Acting upon the observations of Haldane and of Hartridge, which show that the dissociation of CO hemoglobin is markedly increased under the influence of the ultraviolet light, Koza (*Med. Klin.*, 1930, **26**, 422) declares that a similar increase in the elimination of CO can be produced in animals poisoned thereby. In a series of experiments in which the usual methods for resuscitation were employed, including the administration of oxygen, carbon dioxid and respiratory stimulants, those animals which were also exposed to the ultraviolet rays of a quartz lamp showed considerably more rapid recovery than did those not so exposed. Following these experiments, two sisters who had been simultaneously poisoned by CO were observed, the one being treated in the usual manner and the other in precisely the same way with the addition of forty minutes' exposure, during treatment, to the mercury-vapor lamp. The irradiated patient showed a much more rapid elimination of CO and a much more rapid recovery of consciousness than did her sister. The irradiation employed was sufficiently intense to produce as its only unfavorable result a moderate degree of burning of the skin. Although this is the only controlled observation on man, the author finds in other cases evidence that the addition of radiation therapy is beneficial in the treatment of CO poisoning.

Clinical Observations on the Depressant Action of Insulin Upon the Genital Organs.—Levai (*Med. Klin.*, 1930, **26**, 313) states in detail his observations on 3 patients, 1 man and 2 women, in whom the functions of the genital organs were markedly depressed by the more

or less continued administration of small doses of insulin given for the purpose of improving nutrition. All patients were nondiabetic. In the case of the man impotence was produced, while both women endured periods of amenorrhea. In none of these patients was it possible, by the most searching examination, to discover any organic reason for the disturbances in their sexual functions, and in all 3 spontaneous recovery took place after cessation of insulin. Similar instances have not been found in the literature, but the author is able to support these human observations by references to similar depressant actions upon the sexual organs observed in experimental animals. He believes that insulin probably brings about these effects through a disturbance in the balance between several of the endocrin glands. In view of his findings he warns against the indiscriminate administration of insulin for the purpose of improving nutrition, and definitely opposes its employment when the improvement in nutrition is sought for purely cosmetic reasons.

PEDIATRICS

UNDER THE CHARGE OF

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The Early Diagnosis of Whooping Cough.—McGee (*Va. Med. Monthly*, 1930, **57**, 165) made a positive diagnosis of this disease in 64 cases from the character of the cough, presence of an epidemic or history of exposure, the usual absence of any marked signs of bronchitis, laryngitis and postnasal discharge with a leukocytosis, showing as an absolute and relative increase in lymphocytes. The cough that was considered suspicious was an afebrile one, paroxysmal and spasmodic in character, which increased in intensity and was worse at night, and which failed to respond to usual treatment. White and differential blood counts were made after the child had had the suspicious cough lasting from seven to ten days. In 14 of these cases a negative diagnosis was made after a cough lasting from ten to twenty-one days. In no afebrile disease with cough is there so great a leukocytosis with such a high percentage of lymphocytes. The leukocyte counts in this series varied from 10,000 to 46,000 with an average of 19,273 leukocytes, while from 50 to 90 per cent of lymphocytes were noted with an average of 68.2 per cent.

Whooping Cough; Early Diagnosis by the Cough-plate Method.—Sauer and Hambrecht (*J. Am. Med. Assn.*, 1930, **95**, 263) claim that the cough plate is the best means of early diagnosis. The disease can now be diagnosed before the lymphocytosis and whoop. It is early in the disease that a correct diagnosis is most important because it is then that the pertussis bacillus is present in its greatest numbers, whereas it is seldom found after the whoop has developed. In an analysis of 200 cases, they found that the plate was positive in all but 1 of 53 patients in the catarrhal stage; in 70 of 107 in the paroxysmal

stage and in none of 40 in the period of decline. These figures are in agreement with those published by others. A negative plate does not exclude whooping cough. The two most frequent errors in technique are that plates are not well enough coughed upon or that they are made too late in the disease. It is pointed out that this method of early diagnosis should not be compared with the throat culture in diphtheria. In the latter disease the lesion is accessible and the organisms are constantly present. In pertussis the lesion is not accessible and the causative organism as a rule can be isolated only early in the disease. The chief value of the early diagnosis is that the patient and the susceptible children with whom he has been in contact may be quarantined before they in turn expose others. In this way the incidence and the mortality may be lowered.

Viosterol; Prophylactic and Therapeutic Dosage.—Hess, Dale and Klein (*J. Am. Med. Assn.*, 1930, **95**, 316) state that several factors must be given consideration in the determination of the prophylactic dose. It is obvious from the knowledge of the pathogenesis of rickets that insufficient mineral deposition during fetal life as seen in twins and premature infants, rapidly growing infants and babies with repeated infections and diarrhea, must be given special consideration. From blood chemistry determinations, 10 drops of viosterol in oil a day was the smallest dose that prevented a fall in both calcium and phosphorus from the first to the later months of the first year of life, although in 2 cases under their observation in which there were diarrhea and infection even 20 drops daily was inadequate to prevent a fall in calcium and phosphorus. They had no infant on more than 10 drops of viosterol a day to develop rickets as evidenced by clinical, roentgenographic or blood chemical studies. As regards the optimum therapeutic dose, it was impossible to arrive at a positive conclusion from the small group observed. The degree of rickets must be considered in every case. It was found that mild rickets would heal frequently on a dosage of from 10 to 15 drops of viosterol in oil daily while other cases would require larger doses. In some severe cases 15 and even 20 drops did not prove adequate. Infants on 30, 40, 50 and 60 drops showed uniform healing clinically, chemically and by roentgenogram. Toxic symptoms were not observed in any of the infants during the period of observation. The authors do not wish to state that toxic symptoms may not be produced by large enough doses of viosterol, but their investigation showed a large factor of safety in the administration of larger doses of viosterol, at least over limited periods of time.

The Use of a Modified Drinker Respirator in the Treatment of Asphyxia Neonatorum.—Murphy and Coyne (*J. Am. Med. Assn.*, 1930, **95**, 335) report the use of this apparatus in 5 cases of asphyxia neonatorum, with the result that 2 infants survived and 3 died. They feel that none of these babies would have survived had they not been treated with the mechanical respirator. They doubt if the respirator was responsible for the initiation of the respiration, though it may have had a stimulating effect on the respiratory center. The fairly constant increase in respiratory power exhibited by infants during two periods of observation, indicates that the respiratory supplied adequately the ventilation needs of these infants during the period before their respira-

tory centers began to function. It was not surprising that 3 of the infants succumbed in view of the conditions surrounding their births. As far as could be learned the use of the mechanical respirator played no part in causing these deaths. The 2 infants that survived would in all probability have died had it not been for their prolonged mechanical artificial respiration. At least the mechanical respirator supplied an adequate degree of ventilation over a long period of time. This is the most important point in asphyxia neonatorum. It is of the greatest importance to remove the mucus from the respiratory tract before beginning the operation of the apparatus. The advantages of this method are that it is perfectly safe as has been demonstrated by the authors. In addition it is possible to institute treatment in a few seconds and to maintain it over a prolonged period. Normal rate and depth of respiration can be closely simulated and adequate ventilation can be secured. A temperature can be maintained that throws no undue load on the metabolic activity. Free drainage of the respiratory passages can be maintained by adjusting the position of the child. The old and violent methods of resuscitation are avoided, and the complications incident to them are prevented.

Calcium Therapy During Childhood.—OCHSENIUS (*Münch. med. Wchnschr.*, 1930, **77**, 804) emphasizes the great significance of calcium therapy in pediatrics, especially in the treatment of rickets. The administration of calcium in the form of calcium water is of no particular value because in rickets the organism is not able to absorb the calcium even though the food contains an ample supply. The retention capacity for calcium is increased by ultraviolet irradiation, by cod-liver oil that contains phosphorus, and by viosterol. The author recommends the following combination: 25 gm. of tricalcic phosphate, 0.2 gm. of phosphorus, 5 gm. of viosterol and 250 gm. of cod-liver oil. Of this mixture the child should receive one teaspoonful twice a day. If the rickets is complicated by a neuropathy, spasmophilia results and tetany is either manifest or latent. In these conditions large doses of calcium are of great help, because the calcium quickly counteracts the nervous irritability. The sedative effect of calcium has been demonstrated in experiments. It has also proved helpful in the exudative diathesis, especially in the weeping eczema that is accompanied by pruritus. The itching is dependent on the condition of the nervous system and the administration of large doses of calcium counteracts it. It also has a drying effect on the eczema. Children with asthma and those with relapsing bronchitis may likewise be treated with calcium. A difficulty in calcium administration is its unpleasant taste, which may be disguised by the addition of cocoa.

Scarlet Fever; Second Attacks.—GABRIEL and ZISCHINSKY (*Jahrb. f. Kinderh.*, 1930, **127**, 253) use the term "recurrence" only for the rare cases in which both the development and the clinical picture indicate an exacerbation of an old latent scarlet fever, and in which there is little probability of a new exogenic infection. To all cases in which these conditions are not fulfilled, they apply the term "second attack." In more than 20,000 cases of scarlet fever that were seen by them in a period of seventeen years they found 387 cases of "second attack,"

or a percentage of 1.9. The curves of the frequency of first attacks and second attacks ran approximately parallel. As predisposing factors for the development of second attacks of scarlet fever, there are noted wounds of various sorts, measles, chicken-pox and serum disease. The most common predisposing factor was a recurrence of the first attack. The course of second attacks of scarlet fever is usually more severe than in first attacks and complications are more frequent.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Bismuth in the Treatment of Syphilis.—LEVADITI (*Am. J. Syphilol.*, 1930, **14**, 156). For the past nine years, Levaditi, Fournier and their associates have used bismuth in the treatment of syphilis practically to the exclusion of all other drugs. Levaditi reaffirms his principles previously reported by him, which include: (1) Bismuth has a curative and preventive action in early and late syphilis; (2) it causes the rapid disappearance of the spirochete from the early lesion; (3) it sterilizes the lymphatic glands; (4) it causes a favorable modification of the reactions of the blood and spinal fluid: (5) bismuth exercises a profound and lasting curative action in syphilis—principally because of its delayed elimination; (6) bismuth acts where arsenic fails (in arsenic-resistant cases). To these earlier principles Levaditi has added: (7) Bismuth is superior to arsenical therapy with the exception of the prompter sterilizing qualities of the intravenous arsphenamins; (8) bismuth is absolutely innocuous, providing neither intravenous bismuth nor the water-soluble intramuscular preparation is used; (9) bismuth is superior in its therapeutic properties to mercury, and (10) bismuth therapy is efficacious not only in acquired syphilis but also in hereditary and congenital syphilis. The author devotes considerable space to a discussion of the proper preparation and salt of bismuth to be used. He believes that the most efficacious type is either the insoluble bismuth salts in oil suspension or the fat-soluble compound. The main criteria in choice depend on the formation of bismuth deposits in the body with the subsequent formation of bismoxyl, and the actual amount of metallic bismuth contained in the preparation. He names three classes of bismuth compounds as meriting consideration: (1) The iodo-quinin salts of bismuth; (2) the oxids or oxycarbonates of bismuth, and (3) the fat-soluble derivatives. He favors the use of the latter type of bismuth compound and particularly a-carboxethyl; b-methyl-nonoate of

bismuth (biliposol). Its bismuth content is 0.04 gm. per 1 cc. of the oily solution. Experimentally the curative dose varies from 1 to 2 mg. of metallic bismuth to the kilogram of body weight. The sterilization of local lesions is prompt and its effect on the Meinicke reaction is comparable to the arsphenamins. Clinically the salt is employed in bi-weekly intramuscular doses of 2 cc. of the oil in a series of from ten to fifteen injections. The salt is well tolerated and evidence has been gathered that the radiographic bismuth shadows are more diffuse and less opaque than those of insoluble oily suspensions of bismuth. Renal elimination commences rapidly after the injection and is demonstrable up to one and a half to two months after the cessation.

(The report together with the continental bibliography appended bears evidence that the original enthusiasm of Levaditi and his associates in the exclusive use of bismuth has not declined.)—EDITOR.

GYNECOLOGY AND OBSTETRICS

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Hysterosalpingography.—In a well-presented and excellently illustrated article, WITWER, CUSHMAN and LEUCUTIA (*Am. J. Roentgenol.*, 1930, **23**, 125) present their views on the present status of hysterosalpingography as a diagnostic measure. They assert that the use of iodized oil for outlining the female genital organs is a simple and safe procedure, since in a series of 512 cases the only accident observed was that of a ruptured tube, which did not lead to any ill effects. The method is of great diagnostic value in developmental anomalies of the genital organs, in tubal conditions leading to sterility, in certain carefully selected cases of pregnancy in which therapeutic abortion is indicated or a differential diagnosis from other obscure conditions is essential, in uterine tumors excepting malignant ones and in certain extrauterine neoplasms. The contraindications to the use of the method are recent hemorrhage, inflammatory conditions that are not completely quiescent, active infections or malignant growths involving the cervix, previous intrauterine interventions; ectopic gestation or intrauterine gestation in which a therapeutic abortion is not desired, infected cervical or uterine polyps and fever. In certain instances the injection of iodized oil is of direct therapeutic value. The most important practical value of hysterosalpingography in connection with extrauterine tumors is in the differentiation between these and large uterine

fibromas, when an accurate diagnosis cannot be made by the usual methods of gynecologic examination. It is advisable in such instances to outline the margin of the tumor by a lead wire placed on the abdominal wall during the taking of the roentgenogram and then to analyze the relation of the uterine cavity to the lead wire. If the uterine cavity appears of normal shape and size, but on the periphery of the lead wire, the condition is that of a cyst, while if the uterine cavity is enlarged, distorted and appears in the center or near the center of the lead wire, the condition is that of a uterine fibroma. The addition of roentgenograms in the lateral view will occasionally aid in further substantiating the diagnosis. They describe their technique in detail which is generally similar to that used by most other workers in this field and is extremely simple.

Results of Treatment in Cancer of the Cervix.—In a most comprehensive statistical study, embracing the material of many of the larger European clinics, FELDWEG (*Zentralbl. f. Gynäk.*, 1930, **54**, 779) has presented the results which have been attained by the various methods of treatment in most of the usual types of carcinoma of the female genital organs. In looking over his tables concerning carcinoma of the cervix, it is seen that whereas operation has given an absolute cure rate of less than 20 per cent in over 5000 cases, irradiation is somewhat better, but the combination of operation and irradiation is probably the best of all, giving absolute cure rates varying from 18 to 27 per cent. These figures may seem low to some of our readers, but it must be remembered that they refer to absolute cure, that is, the number of patients cured out of the total number seen, irrespective of the fact that many of the cases were beyond help and were given no treatment. When we come to the relative cures, that is, the number of cures obtained from the number of patients actually treated, naturally the figures are much more promising. In this classification we find that operation alone gives 35 per cent and operation plus irradiation or irradiation alone give about the same results, except in Heyman's statistics, where irradiation gives over 46 per cent relative cures. These statistics of relative cures apply only to the so-called operable cases, and it is well known that operability varies with the individual clinic, as is shown in this study where it varies from 14 to 62 per cent. In spite of the popularity of the Wertheim operation in Germany, the author is of the opinion, as the result of this study, that it should no longer be considered as a standard method of treatment by itself. It is no longer a question of operation *or* irradiation in a given case, but rather should the patient receive operation *and* irradiation or only irradiation.

Biologic Test in Diagnosis of Chorionepithelioma.—The value of the test which has been described by Aschheim and Zondek in the diagnosis of pregnancy seems to be fairly well established. For the benefit of those who may not be familiar with it, the test is based upon the proven fact that pregnant women excrete large amounts of hypophyseal hormone in the urine. When the urine from pregnant women is injected into infantile mice, corpora lutea and hemorrhages are formed in their ovaries. As a result of many tests, it is claimed to be positive in 98 per cent of the cases of pregnancy, even in the early days. In cases of

ectopic gestation and abortion the test is positive as long as living fetal tissue is in biologic contact with the blood of the mother. In an article by ASCHHEIM (*Am. J. Obst. and Gynec.*, 1930, **19**, 335), who is one of the discoverers of the test, in addition to emphasizing the value of the test in the types of cases mentioned, he states that the test has been found strongly positive in hydatidiform mole and in chorionepithelioma. In one instance it was twelve times stronger than the reaction usually obtained in the second month of gestation (measured by the minimum dose of urine, which gave a positive mouse test). Since there is no embryo in hydatidiform mole, it must be the living tissue of the mole that is responsible for the reaction. He feels that one should make this test whenever there is a clinical suspicion of chorionepithelioma and always after a hydatidiform mole has been expelled. The test, however, may remain positive after hydatidiform mole as long as two months without evidence of chorionepithelioma, so that this must be taken into consideration.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Meatless Diet as a Therapeutic Measure in Ménière's Disease.—Ménière's disease is characterized, in the order of their appearance, by tinnitus aurium, severe vertigo, nausea, vomiting and in many cases deafness. These symptoms usually reach their height within an hour and then slowly disappear in reverse order. Because Ménière's historical case (1861) was associated with intralabyrinthine hemorrhage, this lesion for a long time was regarded as the sole cause of the condition. It is now recognized that the symptoms may be due to a variety of infectious and metabolic states and vascular derangements affecting the vestibular (and often the cochlear) mechanism directly or indirectly. For this reason, and because vertigo is its outstanding symptom, many instances of vertigo have been regarded erroneously as Ménière's disease. Therefore, it is important that a proper diagnosis be made, so that a clearer conception of the etiology, pathology, prognosis and treatment be obtained. Consequently, any contribution tending to clarify our none too concise ideas of Ménière's disease should be welcomed. In this connection, MUCK (*Klin. Wchnschr.*, 1930, **9**, 491) offers a diagnostic and a therapeutic suggestion. Interpreting the vasostrictor nasal reflex—as manifested by the "mucographia alba" and produced by applying epinephrin to the mucosa of the turbinal—as an indication of altered intracranial vascular innervation, the author regards its presence in Ménière's disease as proof of a causal angiospasm of the auditory artery. Because the same reflex has been produced in epilepsy and in migraine, and because both of these conditions have responded in certain instances to a meatless diet, the author withdrew meat from the diets of several patients suffering from recurrent attacks of Ménière's disease. Those who strictly adhered to the right dietary régime were improved.

Analogies in Picture in Otosclerosis and Juvenile Diseases of Epiphysis.—Investigators into the cause and nature of otosclerosis have remarked about its occasional association with certain conditions of abnormal osseous development, such as osteogenesis imperfecta, and have observed a histopathologic similarity between otosclerosis and some types of diseases of bone, notably the localized forms, osteodystrophia fibrosa (ostitis fibrosa). In this connection we take the liberty to quote from the *Journal of the American Medical Association* (1930, **94**, 2033) that LEIRI (*Finska läk.-sällsk. handl.*, 1930, **72**, 206) "asserts that many and important features are seen in both disorders" (otosclerosis and juvenile diseases of epiphysis). "He expressly states that mechanical irritation, while it plays a significant part in the development of otosclerosis, is no more the primary cause in otosclerosis than in juvenile diseases of the epiphysis."

Mixed Tumors of Palate.—Mixed tumors of the palate present the same distinctive histologic complexities and clinical benignancy as those occurring in other oral-fascial structures, especially the parotid gland, of which they constitute the characteristic neoplasm. Palatal mixed tumors are rare. Probably less than 100 cases are on record. Of these approximately one-half have been encountered in the soft palate. D'AUNOY (*Am. J. Path.*, 1930, **6**, 137) reports 2 cases of palatal mixed tumor in females, aged twenty-five and forty-three years respectively. In the younger individual the new growth occupied the soft palate. SONNENSCHEIN (Mixed Tumors in the Soft Palate: Reports of Two Cases and a Survey of the Recent Literature, *Arch. Otolaryngol.*, 1930, **11**, 137) also describes 2 mixed tumors which were removed from the soft palates of 2 men, each twenty-nine years of age. Both authors recognize the theory of embryonal enclasement as a satisfactory explanation of the origin of these tumors. Furthermore, they agree that they are essentially benign, even though the microscopic picture is often suggestive of malignancy. Each writer, too, calls attention to the likelihood of local recurrence, particularly after incomplete surgical removal. Treatment consists in operative ablation, except when the growth involves vital structures. When surgical intervention is contraindicated roentgen therapy is said to be efficacious.

A Consideration of Peritonsillar Abscess With a Rational Surgical Method of Relief.—In peritonsillar abscess one meets a condition sufficiently common in occurrence, painful and debilitating in its course, serious in its complications and sequelæ and refractory of customary therapeutic measures to command the utmost respect and attention. As a rule, it is apparent that the prevailing operative approach *via* the palate leaves much to be desired in the surgical management of many of these cases. By taking advantage of a more natural point of access to those peritonsillar abscesses situated in the supratonsillar fossa, DOBBS (*Laryngoscope*, 1930, **40**, 186) describes a method whereby the successive insertions of graduated screw instruments in the cleft beneath the plica semilunaris affects adequate evacuation and drainage of the pus with a minimum amount of pain, hemorrhage and danger to the patient. A companion article by PELZ (*Ibid.*, p. 190) elaborates the instrument and site of approach.

RADIOLOGY

UNDER THE CHARGE OF

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The Status of Ultraviolet Ray Therapy in Diseases of the Skin.—From a review of the literature and his own experience, SCHILLER (*Radiology*, 1930, **14**, 576) arrives at the opinion that very few skin diseases can actually be treated with greater benefit by the ultraviolet rays than by other measures. Those which can are the tuberculous lesions of the skin and the group of septic conditions including septic wounds and ulcers. In other groups the ultraviolet ray has proved to be either a more or less indifferent agent or, at best, an adjunct to general treatment. While the use of ultraviolet in proper hands is accompanied by a minimum amount of risk it is not as foolproof as some believe, and cannot be put into the hands of the public for indiscriminate application. For example, superficial ulcerations which heal slowly and leave a suspicion of malignancy can be produced by overdosage, and many cutaneous diseases are aggravated by light.

The Value of a Lateral View in the Diagnosis of Pregnancy.—For the roentgenologic diagnosis of early pregnancy and multiple pregnancy GRIER (*Radiology*, 1930, **14**, 571) considers the lateral view to be decidedly more reliable than anteroposterior. When a pregnant woman lies on her side the uterus occupies the anterior part of the abdomen and the total dimension of the tissue to be penetrated by the rays is considerably less than when she lies on her back, and a clearer image of the fetus is obtained. In the later months of pregnancy, after the fetal head has descended into the pelvis the anteroposterior view is preferable.

Phytobezoar in the Stomach.—In 1928 Maes collected 139 cases of bezoars, of which 23 were phytobezoars. Of the latter, persimmon-seed balls seem to be most common, probably because of the high percentage of gum and pectin in such masses. CAMP (*Am. J. Roent. and Rad. Therap.*, 1930, **23**, 413) reports an additional case. The patient had been well until two and a half months previously, at which time he had eaten a large quantity of persimmons. Gradually he began to have epigastric distress with a sensation of pressure and grinding about three hours after meals. In view of the history a persimmon-seed ball was suspected clinically. The roentgenologic examination with the barium meal revealed an extensive mottled central defect in the gastric shadow, characteristic of a bezoar. At operation the mass of persimmon seeds was found to be 15 cm. in length and 5 cm. in diameter. There was also a subacute gastric ulcer, with a shallow crater, on the posterior wall just below the angle.

Echinococcic Involvement of Bone.—Echinococcus cysts in man occur rarely in the United States and Canada, and the bones are involved in less than 2 per cent of the cases. STONE (*Radiology*, 1930, **14**, 557) reports an instance in which the cysts were situated in the ilium and sacrum. Starting as a small cyst, echinococcus involvement of bone develops into a multilocular cyst with many small ones in the immediate vicinity. There is no sequestration, no atrophy and no increased calcification. Any bone may be affected, but the pelvis, femur, humerus and tibia are the commonest sites.

In the same issue of *Radiology* (p. 562) Hsieh reports a case observed at Peiping, China, in which the pelvic bones and the head and neck of the right femur were involved.

Observations on the Clinical Value of the Roentgen Ray in the Diagnosis of Cardiovascular Disease.—The Roentgen ray affords by far the most accurate measurements of heart size and shape that can be obtained, in the opinion of WHITE (*Am. J. Roent. and Rad. Therap.*, 1930, **23**, 353). In the presence of obesity, emphysema and other complications which render physical examination of the heart very imperfect, the Roentgen ray sometimes affords the only means of determining heart size and shape. Surprising and unexpected findings, such as pericardial calcification or aneurysm of the aorta are sometimes revealed only by Roentgen study. The size of the aorta and of the left auricle, occasionally also of the left ventricle, can be determined only by the Roentgen ray. Abnormalities of the hilus shadows and of the pulmonary artery are important findings which can be discovered only with the Roentgen ray. Observation of peculiarities in pulsation of the heart and great vessels is alone worth the trouble of applying this method of study.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Unusual Case of Cerebrospinal "Giant Cocci" Meningitis.—WEINBERG (*J. Nerv. and Ment. Dis.*, **71**, 412) observed a case in which no typical meningococci were found, but after repeated examinations "giant cocci" were found. The patient recovered rapidly following the administration of 10 cc. of antimeningococcic serum intracisternally, whereas treatment by the lumbar and intravenous routes had been unsuccessful. The author believes that large doses of serum are not necessary in the treatment of meningitis, and that repeated lumbar puncture may do considerable damage. The bacteriologic discussion is presented by Robert Koch.

Syndromes of Tumors in the Chiasmal Region.—DEERY (*J. Nerv. and Ment. Dis.*, 1930, **71**, 383) presents 170 cases receiving a transfrontal operation which presented clinical evidence of "chiasmal syndrome." The cases are recorded as follows: Pituitary adenomas, 54; craniopharygeal pouch cysts, 47; suprasellar meningiomas, 16; cases with negative findings, 15; giomas of the optic chiasm, 14; question of chronic arachnoiditis, 13; third ventricle tumors, 4; aneurysm, 3; cholesteatomas, 2; sphenoidal ridge meningioma, 1; angiomatous malformation, 1. The preoperative and postoperative diagnoses are compared with a view to clarifying the differential diagnoses between the various subgroups. Pituitary adenomas had been misdiagnosed as craniopharyngeal pouch cysts in 9 cases; supracellar meningiomas in 7; olfactory groove meningioma in 1; third ventricle tumor in 1. Of the 9 cases considered to be craniopharyngeal pouch cysts, 3 showed suprasellar calcification and 1 showed intrasellar calcification, indicating that calcification does occur at times in pituitary adenomas. Cases misdiagnosed as suprasellar meningiomas all showed suggestive evidence of dyspituitarism. "If a middle-aged person presenting this differential problem shows a perfectly normal sella and no signs of pituitary dysfunction, one can reasonably expect to find a small meningioma. If either sellar changes or signs of pituitary dysfunction are present the diagnosis is a little less safe to make. On the other hand, as already stated, all adenomas need not markedly change the sella." Anosmia and uncinate attacks led to the diagnosis of one pituitary adenoma as olfactory groove meningioma, although characteristic mental findings were absent. As to this group, the author believes that clinical evidence of the dyspituitarism when found is unsafe to disregard; a normal appearing sella or calcification within or above it are both found in patients with pituitary adenoma; a large adenoma with widely distended sella may occur at a very early age; either homonymous field defects or choked disks may occasionally be caused by adenomas. The craniopharyngeal pouch cysts showed a rather typical history of gradual dimness of vision and frontal headaches over a period averaging two years. Visual defects were present in all cases with asymmetrical defects as a rule. Complete blindness occurred in 1 and good vision in both eyes in 1. Practically all of these cases showed evidence of pituitary insufficiency, and suprasellar calcification occurred in 72 per cent. Twelve cases were incorrectly diagnosed before operation. The other lesions causing the chiasmal syndrome are analyzed in a somewhat similar way. The author calls attention to the fact that there is a strong clinical similarity between the groups, and there is considerable possible variation in the syndrome itself.

The Rôle of Psychical Factors in the Production of Organic Nervous Disease.—RABINER and KESCHNER (*J. Neurol. and Psychopathol.*, 1930, **10**, 311) state that many patients who are djagnosed as functional later show undoubted evidences of organic nervous disease. This raises the question as to what relationship may exist between the functional and organic syndromes presented. The clinical experience of these authors suggest to them that some organic nervous diseases may occur in two phases, the early, psychic, and the later, organic; that the transition between these two phases is imperceptible and can only be

appreciated when patients remain under prolonged observation by the same observers. They briefly review the literature on the influence of function on structure, and present a thesis that abnormal lipoid metabolism due to psychic factors may produce structural changes in the central nervous system which may account for the organic clinical picture manifested later. They present briefly three cases which were diagnosed as functional in the beginning and later developed dystonia musculorum deformans. (The thesis presented is general in its implications, but the evidence cited applies only to this particular organic disease.)

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Radiogenic Microcephaly: A Survey of Nineteen Recorded Cases, With Special Reference to Ophthalmic Defects.—GOLDSTEIN (*Arch. Neurol. and Psychiat.*, 1930, **24,** 102) observed severe disturbances of the central nervous system of children irradiated *in utero*. Of 75 children so exposed, 20 (26.6 per cent) exhibited marked defects, 18 (24 per cent) being microcephalic idiots. In previous papers the conclusion is reached that pelvic radiotherapy during pregnancy is extremely injurious to the fetus. The ocular defects of 19 children whose defects were believed to be due to irradiation *in utero* were thought to be due to inhibitions of development of the central nervous system, as manifested by microcephaly at or shortly after birth. Sixteen women were treated with the Roentgen ray, 2 with radium and 1 with mesothorium, relatively large doses being given to all the women. Many of them received more than one Roentgen treatment. Fifteen women received radium therapy during the first four months of gestation, and several of them were given one or more treatments in the first month. The indications for radium therapy were pelvic disease, tuberculosis, peritonitis, functional metrorrhagia, amenorrhea and sarcoma of the ovary. In 2 women abortion was attempted by the use of the Roentgen rays. Reports were available concerning ocular defects in 15 of the 19 children born to these 16 mothers. The various eye disturbances were given as ankyloblepharon, 3; bilateral chorioretinitis, 2; optic atrophy, 3; strabismus, 5; nystagmus, 2; microcornea, cataract, defect in the retina, abnormal retinal pigmentation, albinic fundus and epicanthus, each once. Some children exhibited more than one defect. Microphthalmia was present in 7 children. Other optic defects were associated with the microphthalmia. Four children were almost completely amaurotic, the blindness being due to optic atrophy, chorioretinitis or to both.

It is known that of 15 children exposed to irradiation in the first four months of gestation, 11 (73.3 per cent) manifested disturbances of the eye. The remaining 4 children were irradiated for the first time during or after the fifth months of gestation. It was observed that of the 14 microcephalic children who had the round, small type of head, 8 (57 per cent) manifested disturbances of the eye while 3 (21 per cent) did not. The probable connection between fetal irradation, malformation of the skull and the occurrence of ophthalmic defects is a matter for later discussion.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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An Epidemic of Influenza in an Isolated Community—Northwest River, Labrador.—SMILLIE (*Am. J. Hyg.*, 1930, **11**, 392) studied an epidemic of influenza which occurred in Northwest River, an isolated community in Labrador, in 1928. The date of introduction of the disease into the community was known and it was possible to trace the epidemic throughout its course. It seems probable that the virulence of the infective agent remained fixed, and the dosage was uniform. There occurred, however, a marked variation in resistance of various individuals to infection. It seems probable that this resistance was nonspecific. The infective agent disappeared completely from the community in a short time, for a presumably highly susceptible group of Indians entered the community one month after the last case had occurred and none of them were affected.

Effect of Repeated Daily Exposure of Several Hours to Small Amounts of Automobile Exhaust Gas.—The Public Health Service (*Pub. Health Rep.*, 1929, **44**, 1260) gives the following data on the effect of carbon monoxid in gasoline engine exhaust gas: *With the subjects at rest or exercising mildly:* (1) Exposure to 2 parts of CO in 10,000 caused: (*a*) in 2 hours, slight but not discomforting symptoms in some subjects; (*b*) in three and a half to four hours, distinct frontal headaches of a discomforting nature in some subjects; (*c*) in six and a half hours no occipital headaches occurred in any subjects and no symptoms of any kind were experienced in 50 per cent of the exposures; (*d*) in three and a half to four and a half hours a blood saturation of 20 per cent; (*e*) in five to six hours a blood saturation of 25 per cent. Saturation above 25 per cent was attained very slowly. (2) Exposure to 3 parts of CO in 10,000 caused: (*a*) in less than two hours slight symptoms in some

subjects; (*b*) in two and a half to three hours distinct frontal headaches in some subjects; (*c*) after three hours a few occipital headaches and cases of vertigo; (*d*) in five hours distinct discomforting symptoms in more than 65 per cent of the subjects; (*e*) in two and a half to three and a half hours a blood saturation of 20 per cent; (*f*) in three to four hours a blood saturation of 25 per cent; (*g*) in four to four and three-quarter hours a blood saturation of 30 per cent. (3) Exposure to 4 parts of CO in 10,000 caused: (*a*) in one and a half to two hours frontal headaches, in some subjects; (*b*) in two and a half to three and a half a few occipital headaches; (*c*) in three and a half to four hours more than 90 per cent had distinct frontal headaches. (*d*) in one and a half to two and a half hours a blood saturation of 20 per cent; (*e*) in two and a half to three and a half hours a blood saturation of 25 per cent; (*f*) in three to four hours a blood saturation of 30 per cent. (4) The results of the control tests showed that a few cases of headache occurred, but the number was probably no greater than might be expected in any group of normal men. There was no distinct difference in the character and number of symptoms when exhaust gas was entirely absent from the air as compared with experiments when the air contained exhaust in which the CO was reduced to an insignificant amount by carbureter adjustment. Although there was a tendency for headaches to appear with a lower amount of CO hemoglobin when the latter was attained by exposure to the lower concentrations of carbon monoxid, in general, frontal headaches began in some subjects only when the saturation reached 18 to 20 per cent. A few occipital headaches accompanied by vertigo distinctly occurred at 23 to 28 per cent. *With exercise:* even though of a mild form, exercise distinctly augmented the absorption of CO and caused symptoms to appear after shorter exposure. Exercise immediately after exposure markedly increased the speed of elimination, but this procedure is not recommended or advised as a treatment for poisoning by CO. Until the supply is exhausted, single copies of this bulletin may be had free upon application to the Surgeon General, United States Public Health Service, Washington, D. C. Additional copies may be purchased from the superintendent of Documents, Government Printing Office, Washington, D. C., at 15 cents per copy.

Fatty Degeneration of the Liver and Kidneys in the Dog Apparently Associated with Diet.—SEBRELL (*U. S. Pub. Health Rep.*, 1929, **44**, 2697) was feeding dogs a diet designed to produce blacktongue, a condition in the dog which is highly analogous to pellagra in man. Certain of the dogs presented a very extensive and readily recognized fatty degeneration, especially of the liver and kidneys, though they may or may not have presented evidence of blacktongue. The condition could not be recognized by a competent veterinary pathologist, and attempts to transmit it by inoculation failed. The condition seems to be of dietary origin.

The Fate of Tubercle Bacilli in the Organs of Reinfected Rabbits.—LURIE (*J. Exper. Med.*, 1929, **50**, 747) states that in the presence of a certain amount of residual primary lesions, human or bovine tubercle bacilli of reinfection are destroyed in all the organs of rabbits without any preliminary multiplication. This destruction is not quite complete;

a few organisms persist even two months after reinfection. No macroscopic tuberculous lesions due to the reinfection develop in these rabbits. With the practical disappearance of the primary lesions and their enclosed organisms, restricted multiplication of the bovine bacillus of reinfection takes place but not the extensive growth of the virus observed in rabbits after a primary infection. In these rabbits slight tuberculous lesions develop as compared with the massive tuberculosis of primarily infected rabbits. The human tubercle bacillus of reinfection does not multiply at all, nor does it cause any lesions, even when the lesions of the primary infection have almost disappeared. Although the rabbit destroys efficiently considerable quantities of bovine tubercle bacilli of reinfection introduced from without, it may harbor innumerable human bacilli in the residual primary lesions of the lung and kidney.

Pasteurized Dried Fruits.—FELLERS (*Am. J. Pub. Health*, 1930, **20**, 180) claims that dried fruits harbor considerable numbers of molds and bacteria and also a few yeasts. It is desirable to protect the public against bacterial infection from these foods. At least one such outbreak has been reported. Dried fruits, such as dates, raisins, figs, apricots and prunes, may be pasteurized in paper cartons with moist heat at controlled temperatures and humidities. In general, different treatments are required for each fruit and often each variety must be handled a little differently. Temperatures which have been found effective in greatly reducing the total numbers of microörganisms on dried fruits at humidities of 70 to 100 per cent vary from 150° to 185° F. for thirty to seventy minutes. Escherichia coli and Eberthella typhosum were destroyed in every case where the temperature of the fruit remained at 160° F. or above for thirty minutes at relative humidities of 75 per cent or more. Commercial processes for the effective pasteurization of dates, figs and raisins are now being developed or used. Sulphured fruits harbor very few organisms because of the inimical effect of sulphur dioxid. Acid fruits are more easily pasteurized than those of higher pH. From a public health viewpoint, pasteurization marks a definite advance in the merchandising of dried fruits.

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